The American Journal of Medicine

October 1953

The American Journal of Medicine

The American Journal of Medicine is published monthly by *The American Journal of Medicine, Inc.*, 49 West 45th Street, New York 36, N. Y. *Yearly Subscriptions:* $12.00 *U. S. A.*; $13.00 *Canada and Latin American countries*; $15.00 *Foreign. Single Numbers*, $2.00; *Symposia Number*, $4.00. *Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. October, 1953—Volume XV, No. 4.*

MANUSCRIPTS: All manuscripts should be addressed to the Editorial Office of the Journal, 49 West 45th St., New York 36, N. Y. *Style for bibliography:* Doe, J. J. Treatment of hypertension. Am. J. Med., 6: 72, 1948.

Change of address must reach us one month preceding month of issue.

Invitation to asthma?

not necessarily . . .

Tedral, taken at the first sign of attack, often forestalls severe symptoms.

relief in minutes . . . Tedral brings symptomatic relief in a matter of minutes. Breathing becomes easier as Tedral relaxes smooth muscle, reduces tissue edema, provides mild sedation.

for 4 full hours . . . Tedral maintains more normal respiration for a sustained period—not just a momentary pause in the attack.

Prompt and prolonged relief with Tedral can be initiated any time, day or night, whenever needed, without fear of incapacitating side effects.

Tedral provides:

theophylline	2 gr.
ephedrine	3/8 gr.
phenobarbital	1/8 gr.

in boxes of 24, 120 and 1000 tablets

Tedral®

WARNER-CHILCOTT
Laboratories NEW YORK

Conservative living—avoiding unnecessary emotional as well as physical stress, providing real relaxation—and conservative medication are essential parts of the effective management of arterial hypertension.

Theominal—time-tested vasodilator and sedative—is helpful to many thousands of hypertensives. Continuous administration of Theominal often holds the blood pressure at a nearly normal level, relieving the congestive headache, chest pains and vertigo which frequently accompany hypertension.

WINTHROP

THEOMINAL®

(Theobromine 5 grains, Luminal ½ grain)

Vasodilator and Sedative for

ARTERIAL HYPERTENSION

●

When less sedation is required:

new THEOMINAL Ⓜ

(Theobromine 5 grains, Luminal ¼ grain)

WINTHROP-STEARNS INC.

NEW YORK 18, N. Y. • WINDSOR, ONT.

Theominal and Luminal (brand of phenobarbital), trademarks reg. U.S. & Canada

CONTENTS

The American Journal of Medicine

Vol. XV OCTOBER, 1953 No. 4

Editorial

Clinical Studies

The author had opportunity to study an unusually large number of cases (twenty-six) of Wilson's disease. Genetic analysis confirms the previous impression of transmission as an autosomal recessive. Biochemical studies elaborate upon the characteristically excessive urinary excretion of aminoacids and copper, the low serum levels of copper and "copper enzyme" (coeruloplasmin).

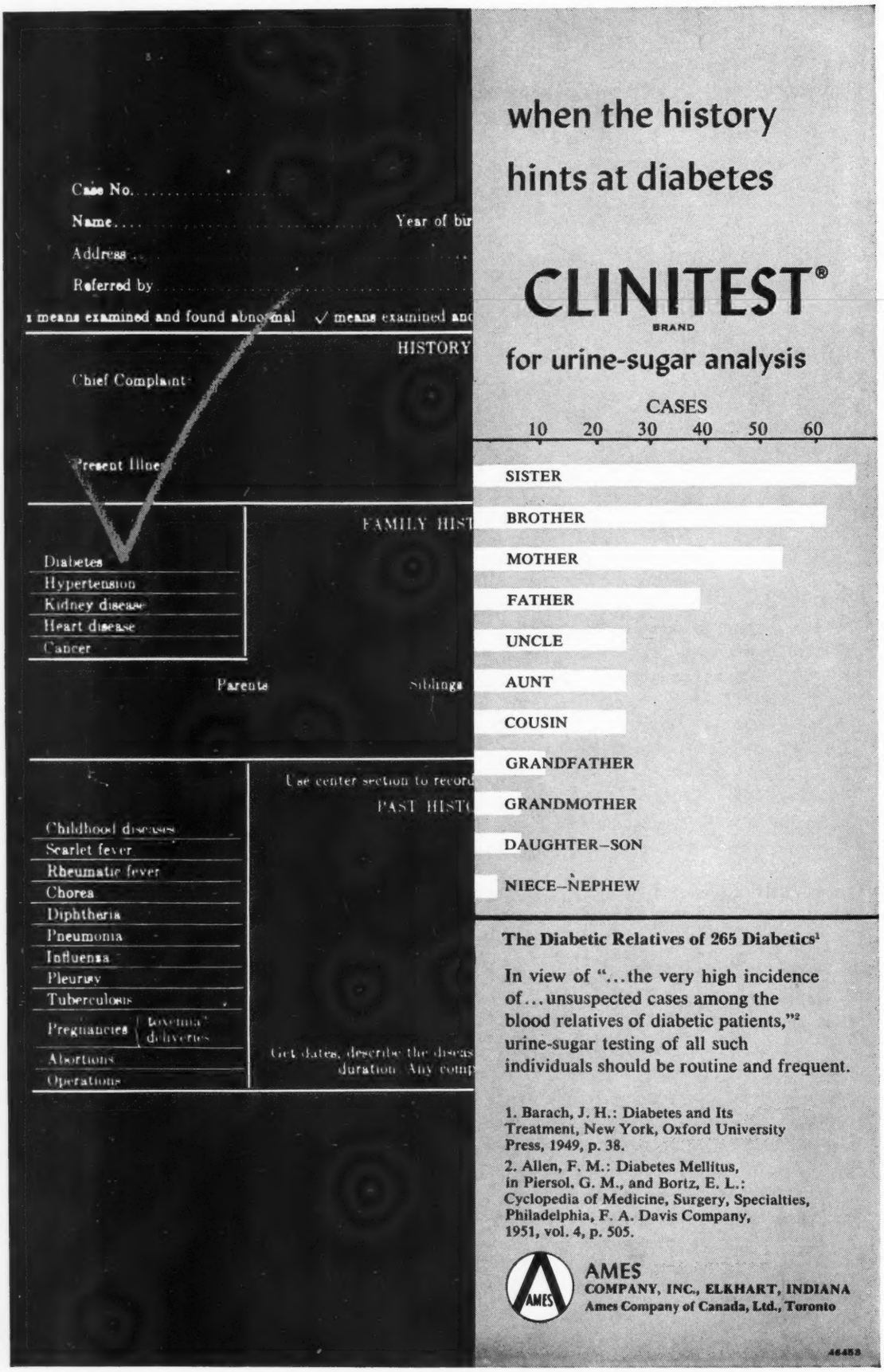
The frequency of sufficient clinical and laboratory evidence of overt liver damage to be of value in the differential diagnosis of Wilson's disease has been a matter of some controversy. In this study of eleven cases, such evidences were found in seven instances and in five of these the indications of hepatic disorder preceded those of neurogenic origin. In some cases the manifestations of hepatic insufficiency dominated the clinical picture.

This post hoc study admittedly is not altogether convincing but nevertheless points up the many reasons why body and plasma stores of potassium may become depleted in chronic alcoholism with malnutrition and how this may play a role in the clinical manifestations. The authors claim good results in the treatment of hepatic coma with oral and parenteral potassium administration.

Pulmonary function studies in patients with pulmonary sarcoidosis reveal an incidence of significant impairment of ventilation and gas perfusion out of proportion to the extent of lung involvement apparent upon physical or roentgenographic examination. Two general patterns, with much overlap, can be discerned: a fibrosis type due to diffuse parenchymal invasion, at first by inflammatory, later by organizing fibrotic and hyalinizing lesions; and an emphysema type due to peribronchial and endobronchial localization, with resultant generalized and bulbous emphysema. Cor pulmonale may be a secondary complication.

In connection with ACTH or cortisone therapy, the authors warn of worsening of pulmonary function in some cases due to apparent acceleration of pulmonary fibrosis consequent upon rapid healing of acute inflammatory sarcoidosis, and activation of incidental inactive tuberculous lesions.

Contents continued on page 5



when the history hints at diabetes

CLINITEST®
BRAND

for urine-sugar analysis

The Diabetic Relatives of 265 Diabetics[1]

In view of "...the very high incidence of...unsuspected cases among the blood relatives of diabetic patients,"[2] urine-sugar testing of all such individuals should be routine and frequent.

1. Barach, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 38.

2. Allen, F. M.: Diabetes Mellitus, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery, Specialties, Philadelphia, F. A. Davis Company, 1951, vol. 4, p. 505.

AMES
COMPANY, INC., ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

46453

CONTENTS

The American Journal of Medicine

Vol. XV OCTOBER, 1953 No. 4

Contents continued from page 3

Contents continued on page 7

Rx SURDON

now available in a single tablet...an effective triple prescription for the control of premenstrual tension and dysmenorrhea

PROGESTORAL®

Each Surdon tablet contains 5 mg. of Progestoral® (ethisterone), the orally effective form of the corpus luteum hormone, for its well-known uterine relaxant and hormonal balancing effect.

THIAMINE HYDROCHLORIDE

In each Surdon tablet there are 15 mg. of thiamine hydrochloride (vitamin B_1)—which aids the liver to inactivate estrogen. Thiamine also provides a boost often needed by these patients.

PHENOBARBITAL

Surdon tablets also contain 15 mg. of phenobarbital (approx. ¼ gr.) to allay apprehension, tension and pain—symptoms from which these patients most frequently seek relief.

One or two Surdon tablets per day during the last seven to ten days of the menstrual cycle will usually suffice. Surdon tablets are packaged in boxes of 30.

Organon INC.
ORANGE, N. J.

ORGANON INC., ORANGE, N. J. W 23
Send me trial supply of Surdon Tablets

*Dr.*_____

_____

_____

T. M.—Surdon

Sur—9M

CONTENTS

The American Journal of Medicine

Vol. XV OCTOBER, 1953 No. 4

Contents continued from page 5

Review

Seminars on Neuromuscular Physiology

Conference on Therapy

Contents continued on page 9

THE RECONSTRUCTIVE IRON TONIC.....

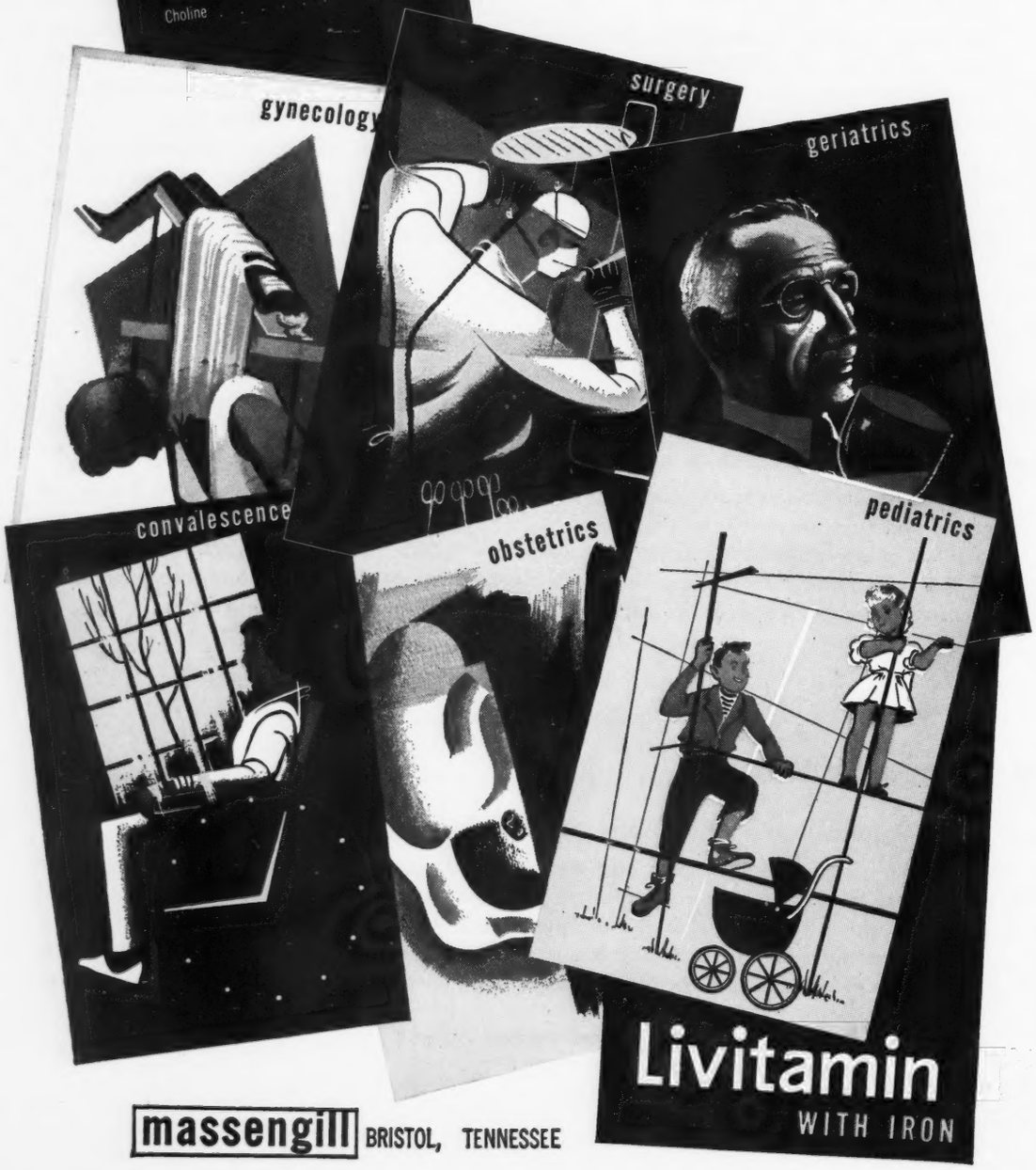
of wide application

Each fluidounce represents:	
Iron Peptonized (Equiv. in elemental iron to 70 mg.)	420 mg.
Manganese Citrate, Soluble	158 mg.
Thiamine Hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (Crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine Hydrochloride	1 mg.
Pantothenic Acid	5 mg.
Liver Fraction 1	2 Gm.
Rice Bran Extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

Provides the multiple requirements for effective treatment of nonspecific asthenia.

The combined therapy is designed to increase appetite and improve the blood picture. Better digestion and improved anabolism are part of the corrective process.

Livitamin is designed to treat the entire syndrome



massengill BRISTOL, TENNESSEE

CONTENTS

The American Journal of Medicine

Vol. XV OCTOBER, 1953 No. 4

Contents continued from page 7

Clinico-pathologic Conference

Case Report

Advertising Index on 3rd Cover

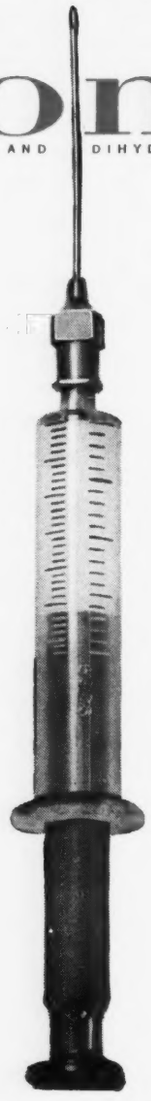
Change of address must reach us one month preceding month of issue.

a new advance in the control of tuberculosis

Drug therapy for the management of tuberculosis continues to advance at a rapid pace. In keeping with the latest improvement—which promises a substantially lower incidence of vestibular and auditory toxicity—Pfizer has made available a new combination of streptomycin and dihydrostreptomycin—

Combistrep*

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN COMBINATION



Recent clinical studies[1] have shown that such a combination, one-half streptomycin and one-half dihydrostreptomycin, gave rise to a significant reduction in neurotoxic side effects as compared to equivalent dosage of either drug used alone, even though administered over the prolonged treatment periods required for the control of tuberculosis.

Combistrep offers these benefits to the tuberculous patient with the further assurance that its purity is of the same high standard typical of all Pfizer pharmaceuticals.

Available in vials of 1 Gm. and 5 Gm., dry powder for preparation of solutions for intramuscular injection.

1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1953.

also,

Streptomycin Sulfate—dry powder and solution

Dihydrostreptomycin Sulfate—dry powder and solution

Streptohydrazid*—a crystalline compound combining streptomycin and isoniazid

Cotinazin®—brand of isoniazid

Viocin* Sulfate—brand of viomycin, for resistant cases of tuberculosis

Pfizer

Pfizer Laboratories, DIVISION, CHAS. PFIZER & CO., INC., BROOKLYN 6, N.Y.

®TRADEMARK

Now, new Donnatal form provides

DEPENDABLE SPASMOLYSIS *plus* Effective B-Complex Therapy

Product Name: **Donnatal Plus**

Characteristics: Combines spasmolytic and sedative actions of Donnatal's natural belladonna alkaloids with phenobarbital, *plus* a full therapeutic quota of important B-complex factors, in three tablets daily.*

Clinical Aspects: Provides effective spasmolytic therapy, *plus* corrective therapy for coexisting deficiencies of important B vitamins.

In fatigue states associated with abnormal carbohydrate metabolism: belladonna alkaloids protect pancreatic islet tissue from vagus overstimulation; phenobarbital decreases psychic factors; B vitamins stimulate appetite and improve absorption and utilization of food.

Helps control gastrointestinal side effects of orally administered antibiotics.

Appearance: Green, sugar coated tablets.

Supply: Bottles of 100 and 1000.

A. H. ROBINS CO., INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878

Donnatal Tablets

Donnatal Capsules

Donnatal Elixir

***Usual daily dose** (3 tablets) **provides:**

hyoscyamine sulfate, 0.3111 mg.
atropine sulfate, 0.0582 mg.
hyoscine hydrobromide, 0.0195 mg.
phenobarbital, 48.6 mg.

plus

B-complex factors

thiamine hydrochloride, 9.0 mg.
riboflavin, 6.0 mg.
nicotinamide, 30.0 mg.
calcium pantothenate, 6.0 mg.
pyridoxine, 1.5 mg.

(Dosage may be doubled, as required)

Robins **DONNATAL PLUS**

Donnatal with B-Complex

A NEW CHEMOTHERAPEUTIC MOLECULE TAILORED SPECIFICALLY FOR REFRACTORY URINARY TRACT INFECTIONS

Discovery of the antimicrobial properties of the nitrofurans provided a novel class of chemotherapeutic agents. These compounds possess specific antibacterial activity with low toxicity for human tissues.

The simplicity and flexibility of this nitrofuran nucleus make possible numerous variations of its chemical and therapeutic characteristics; a remedy may be tailored to fit the disease.

Within recent years we have so designed two important antimicrobial nitrofurans for topical use: Furacin brand of nitrofurazone and Furaspor brand of nitrofurfuryl methyl ether.

Now we have succeeded in chemically tailoring a unique molecule, designed specifically for the treatment of bacterial urinary tract infections:

The NITROFURANS
A unique class of antimicrobials

Products of Eaton Research

FURADANTIN®

Brand of nitrofurantoin:
N-(5-nitro-2-furfurylidene)-1-aminohydantoin.

for **pyelonephritis**
cystitis
pyelitis

which have proven refractory to other antibacterial agents:

FURADANTIN

provides definite advantages:

clinical effectiveness against most of the bacteria of urinary tract infections, *including many strains of Proteus, Aerobacter and Pseudomonas species*

low blood level–bactericidal urinary concentration

effective in blood, pus and urine–independent of pH

limited development of bacterial resistance

rapid sterilization of the urine

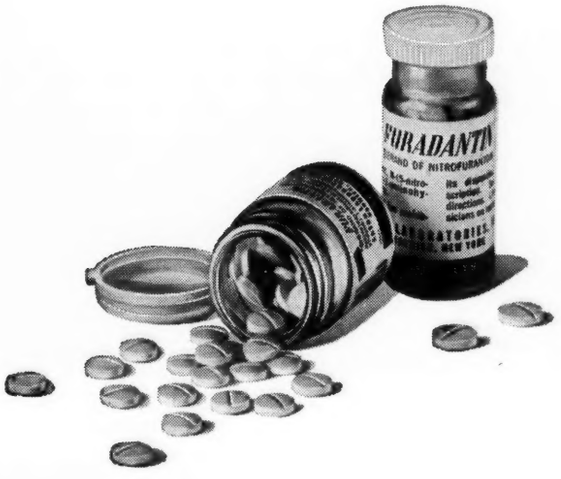
stable

oral administration

low incidence of nausea–*no* abdominal pain–*no* proctitis or pruritus–*no* crystalluria or hematuria

non-irritating–no cytotoxicity–no inhibition of phagocytosis

tailored specifically for urologic use



Scored tablets of 50 & 100 mg.
Now available on prescription
Write for comprehensive literature

EATON LABORATORIES Inc.
NORWICH, NEW YORK

Announcing

A NEW DRUG... for control of blood pressure

UNITENSEN

Brand of Cryptenamine (Irwin-Neisler) TRADE-MARK

Unique Advantages of **UNITENSEN**

- Of all the known Veratrum alkaloids or Veratrum alkaloid preparations, Unitensen, brand of cryptenamine, is the only one which has a 4:1 ratio between its hypotensive activity and the dosage level which produces the side effect of vomiting.
- Unitensen assures a wide margin between therapeutic and vomiting dose by means of a dual biologic standardization for both emetic propensities and hypotensive action.
- Unitensen has a therapeutic index of 125—highest of all available Veratrum alkaloids tested.
- Unitensen has consistent, predictable and uniform action.

COMPARISON OF UNITENSEN WITH PROTOVERATRINE AND THREE OTHER ALKALOID PREPARATIONS

Drug	Emetic: Therapeutic Ratio	Therapeutic Index
UNITENSEN (cryptenamine—Irwin, Neisler)	4:1	125
Protoveratrine A & B	1:1	20
Commercial Alkaloid Preparation A	1.2:1	40
Commercial Alkaloid Preparation B	1:1	—
Commercial Alkaloid Preparation C	1:1	—

Unitensen has shown excellent results in clinical studies in hypertensive crisis, eclampsia, preeclampsia, and preeclampsia with underlying essential hypertension.

Unitensen (Aqueous) is available at present as a parenteral preparation, containing 2 mg. per cc. (260 C.S.R.* Units) of cryptenamine, in 5 cc. multiple dose vials.

*Carotid Sinus Reflex

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Research to Serve Your Practice

Top Flushing Efficiency

plus smooth muscle relaxation in biliary tract disorders with

Cholan *hmb*®

MALTBIE LABORATORIES, INC. · NEWARK 1, N. J.

Maltbie... first to develop American process for converting crude viscous ox-bile into chemically pure dehydrocholic acid

Each tablet contains: **Dehydrocholic acid Maltbie.....250 mg. (3¾ gr.)**
Homatropine methylbromide.....2.5 mg. (1/24 gr.)
Phenobarbital.....8 mg. (⅛ gr.)

COMPARISON SHOWING THE EFFICIENCY OF Cholan *hmb*

TYPICAL AGENT	CLASSIFICATION	EFFECT	FLUSHING EFFICIENCY	COMMENT
Fats or natural bile salts	Cholagogue	Promotes evacuation of the gallbladder	+	Utilizes only bile of normal viscosity present in the gallbladder
Natural bile or unconjugated bile salts	Choleretic	Stimulates secretion of normal bile by the liver	++	Utilizes increased amounts of bile of normal viscosity
Dehydrocholic acid	Hydrocholeretic	Stimulates secretion of fluid bile by the liver	+++	Utilizes copious amounts of free-flowing bile – adequate in absence of spasm of sphincter of Oddi
	Hydrocholeretic, parasympatholytic, sedative	Stimulates secretion of fluid bile by the liver, and relaxes sphincter of Oddi spasm	++++	Utilizes copious amounts of free-flowing bile and relaxes smooth muscle spasm for greater therapeutic efficacy

A new useful combination—

...for antibacterial therapy:

GANTRICILLIN®-300 'Roche.'

Each tablet provides 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the highly soluble, wide-spectrum single sulfonamide.

Gantricillin-300

-a new

antibacterial—

For wide-spectrum, oral
antibacterial therapy --
Gantricillin -300 'Roche'-
Gantrisin plus penicillin
in a single tablet.

AYERST, McKENNA & HARRISON LIMITED • New York, N. Y. • Montreal, Canada

Upjohn

oral
estrogen-progesterone
effective in
menstrual disturbances:

Cyclogesterin
TRADEMARK, REG. U. S. PAT. OFF.
tablets

Each scored tablet contains:

Estrogenic Substances* .. 1 mg.
(10,000 I.U.)

Progesterone .....30 mg.

**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

Available in bottles of 15 tablets.

The Upjohn Company, Kalamazoo, Michigan

In infectious and allergic rhinitis and sinusitis

Biomydrin "is effective as an antibiotic in clearing the nose of pathogenic organisms and purulent secretions. In many cases, sterile cultures were obtained after a brief period of treatment."

Antibiotics & Chemotherapy *3*:299 (March) 1953.

Improvement in 113 of 124 Patients*

Diagnosis	Number of patients	Improved
Chronic catarrhal rhinitis	11	11
Chronic allergic rhinitis	26	25
Right maxillary sinusitis	2	1
Chronic naso-pharyngeal catarrh	6	6
Chronic suppurative sinusitis	3	3
Coryza, Head cold, Catarrhal rhinitis	58	51
Influenza	2	1
Acute catarrh	4	3
Hypertrophic rhinitis	12	12
TOTAL	124	113 (91.1%)

* Eye, Ear, Nose and Throat Monthly *32*:512 (Sept.) 1953.

BIOMYDRIN

'BIOMYDRIN' AND 'THONZONIUM BROMIDE' ARE TRADEMARKS OF NEPERA CHEMICAL CO., INC.

The Biomydrin formula

THONZONIUM BROMIDE 0.05%. Synthesized in the Nepera laboratories. Exceedingly potent antibacterial. Greatly enhances the antibiotic activity of neomycin and gramicidin. Reduces surface tension, facilitating spreading and penetrating. Mucolytic.

NEOMYCIN SULFATE 0.1%. Effective against gram-positive and gram-negative organisms.

GRAMICIDIN 0.005%. Effective against gram-positive organisms.

PHENYLEPHRINE HCl 0.25%. Widely preferred vasoconstrictor.

THONZYLAMINE HCl 1.0%. *Therapeutic concentration* of this effective antihistaminic aids in controlling local allergic manifestations.

- Prompt, prolonged shrinkage of nasal mucosa without secondary congestion.
- pH is 6.2. Isotonic and buffered.
- Does not interfere with ciliary activity.
- Spray covers larger area than could be reached by drops.
- Available on prescription only.

DOSAGE: Adults—2 or 3 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician. Children—1 or 2 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician.

Nepera Chemical Co., Inc. Pharmaceutical Manufacturers, Yonkers 2, N. Y.

when she's Imprisoned by FATIGUE

. . . you may free her from iron-deficiency anemia by the simple expedient of prescribing one IBEROL tablet t.i.d.

As you can see by the formula, three IBEROL tablets provide a therapeutic dose of iron plus seven B complex factors including B_{12}. In addition, IBEROL supplies standardized stomach-liver digest and ascorbic acid.

Compressed, triple-coated IBEROL tablets are easy to take with no trace of liver odor or taste. The outer sugar-coating masks the iron, gives the tablet a pleasant odor and flavor.

For prophylaxis in pregnancy, old age or convalescence, one or two tablets daily are usually enough. May be used as a supplemental hematinic in pernicious anemia. IBEROL is available in bottles of 100, 500 and 1000. Abbott

THREE IBEROL TABLETS: the daily therapeutic dose for adults, supply:

Ferrous Sulfate, U.S.P.	1.05 Gm.
(representing 210 mg. elemental iron, the active ingredient for the increase of hemoglobin in the treatment of iron-deficiency anemia)	
Plus these nutritional constituents:	
Thiamine Mononitrate (6 times MDR*)	6 mg.
Riboflavin (3 times MDR*)	6 mg.
Nicotinamide (2 times RDA†)	30 mg.
Ascorbic Acid (5 times MDR*)	150 mg.
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid	6 mg.
Vitamin B_{12}	30 mcg.
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

prescribe

IBEROL®

(Iron, B_{12}, Folic Acid, Stomach-Liver Digest, With Other Vitamins, Abbott)

1-98

When diet restriction limits nutrition

Vitamins alone are not always enough

Based on the well recognized concept of interrelationship in nutrition, "Clusivol" Capsules offer an extensive formulation of vitamins, minerals, and trace elements . . . factors likely to be lacking when restrictive diets are prescribed.

Multiple vitamin-mineral supplement

REDUCING DIETS
DIABETIC DIETS
GERIATRIC DIETS
POSTOPERATIVE DIETS
PEPTIC ULCER DIETS
LOW SODIUM DIETS
HEPATIC DISEASE DIETS
RHEUMATIC FEVER DIETS

2 "Clusivol" Capsules (average daily dosage) provide:

Vitamin A (synthetic)	25,000	U.S.P. Units
Vitamin D (irradiated ergosterol)	2,000	U.S.P. Units
Vitamin C (ascorbic acid)	150.0	mg.
Thiamine HCl (B_1)	10.0	mg.
Riboflavin (B_2)	5.0	mg.
Pyridoxine HCl (B_6)	1.0	mg.
Panthenol, equivalent to of calcium pantothenate	10.0	mg.
Vitamin B_{12} U.S.P. (crystalline)	2.0	mcg.
Folic acid	2.0	mg.
Nicotinamide	100.0	mg.
Vitamin E (as mixed tocopherols natural)	10.0	mg.
Inositol	30.0	mg.
Choline—from choline bitartrate	30.0	mg.
Biotin	0.1	mg.
d-Methionine	20.0	mg.
Cobalt—from cobalt sulfate	0.1	mg.
Copper—from copper sulfate	1.0	mg.
Fluorine—from calcium fluoride	0.025	mg.
Iron—from 4 gr. ferrous sulfate exsic.	76.2	mg.
Calcium—from dicalcium phosphate	165.0	mg.
Manganese—from manganous sulfate	1.0	mg.
Iodine—from potassium iodide	0.15	mg.
Molybdenum—from sodium molybdate	0.2	mg.
Potassium—from potassium sulfate	5.0	mg.
Zinc—from zinc sulfate	1.2	mg.
Magnesium—from magnesium sulfate	6.0	mg.
Phosphorus—from dicalcium phosphate	127.4	mg.

"CLUSIVOL"® CAPSULES

No. 293—Supplied in bottles of 100 and 1,000.

Ayerst, McKenna & Harrison Limited
New York, N. Y. • Montreal, Canada

Ayerst

WHY TAKE CANDY FROM A BABY?

The overweight patient likes to indulge in sweets. Why not take advantage of this penchant when you prescribe an appetite depressant? ADJUDETS are candy-like troches. They contain d-amphetamine phosphate and essential vitamins, effective aids in reducing regimens Your patient will like this delightfully flavored "sweet." Only 15 calories per troche.

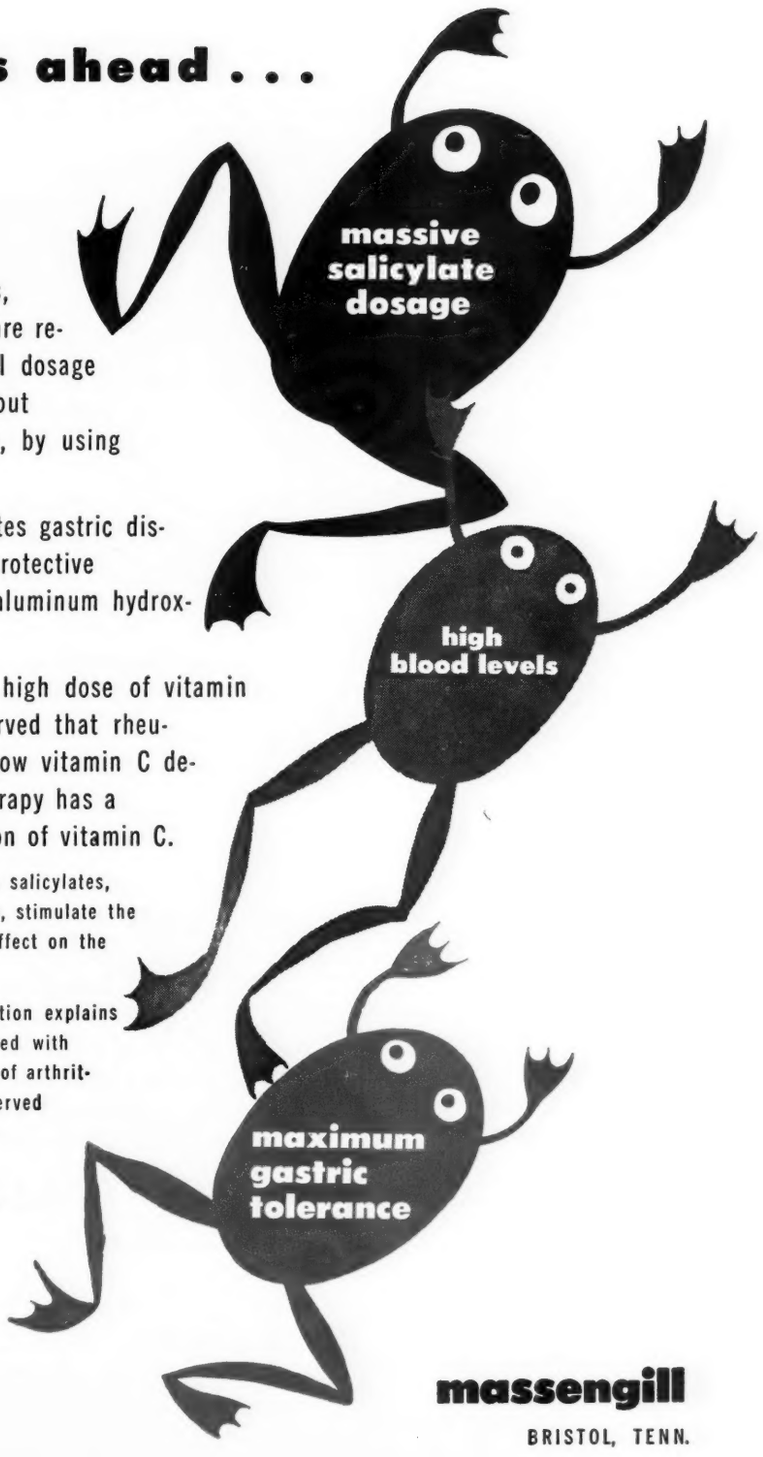
ADJUDETS®

D-AMPHETAMINE-MULTIVITAMIN TROCHES

Supplied: Jars of 36

Wyeth®
Philadelphia 2, Pa.

IN ARTHRITIS
three jumps ahead . . .



MASSIVE DOSAGE

To obtain maximum results, high salicylate blood levels are required. This means high oral dosage which can be attained, without excessive gastric disturbance, by using Salcedrox.

Salcedrox virtually eliminates gastric disturbance, because of the protective combination with activated aluminum hydroxide and calcium carbonate.

Salcedrox also contains a high dose of vitamin C, because it has been observed that rheumatic and arthritic states show vitamin C deficiencies, and salicylate therapy has a tendency to intensify depletion of vitamin C.

There is significant evidence that salicylates, through action on the hypothalamus, stimulate the pituitary, producing an ACTH- like effect on the adrenal cortex. *

This new concept of salicylate action explains many of the clinical results obtained with salicylate therapy in the treatment of arthritides and rheumatic afflictions—observed results that cannot be attributed to analgesic action alone.

*Proceedings Soc. Exp. Bio. Med., 1952, v80, 51-55, G. Cronheim, et al.

FORMULA

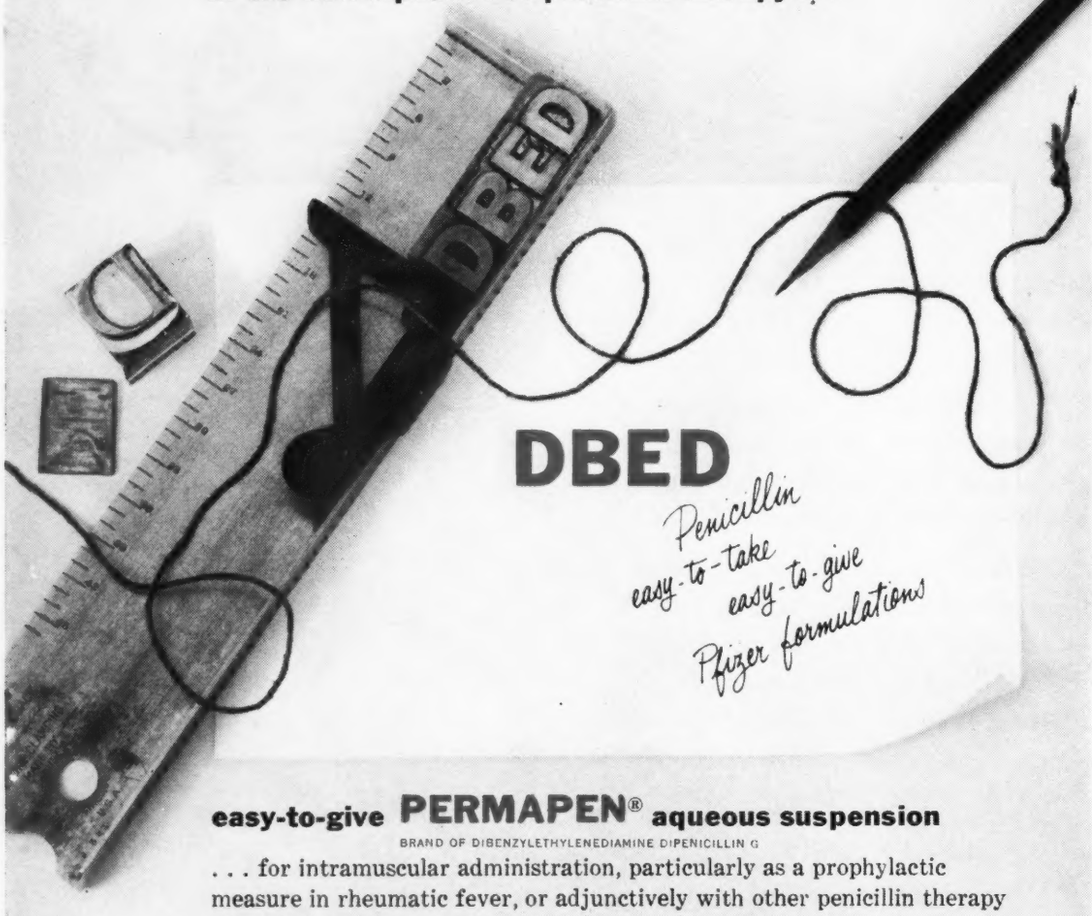
Sodium Salicylate....5 gr. (0.3 Gm.)
Aluminum Hydroxide Gel. dried.....2 gr. (0.12 Gm.)
Calcium Ascorbate.....1 gr. (60 mg.) (equivalent to 50 mg. Ascorbic Acid)
Calcium Carbonate....1 gr. (60 mg.)

massengill
BRISTOL, TENN.

send for professional literature

SALCEDROX

In the new alphabet of penicillin therapy . . .



DBED

Penicillin
easy-to-take
easy-to-give
Pfizer formulations

easy-to-give PERMAPEN® aqueous suspension

BRAND OF DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

. . . for intramuscular administration, particularly as a prophylactic measure in rheumatic fever, or adjunctively with other penicillin therapy of sensitive infections. Levels lasting as long as 14 days from one injection. Supplied in single-dose STERAJECT® disposable cartridges containing 600,000 units of DBED penicillin each with sterile foil-wrapped needle. For use with your Pfizer Steraject syringe.

PERMAPEN® FORTIFIED

BRAND OF DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

aqueous suspension

. . . multiplies therapeutic benefits with the combined higher blood levels of 300,000 units procaine penicillin and the sustained blood levels of 300,000 units DBED penicillin. Supplied in single-dose disposable STERAJECT cartridges each with sterile foil-wrapped needle.

easy-to-take PERMAPEN® oral suspension

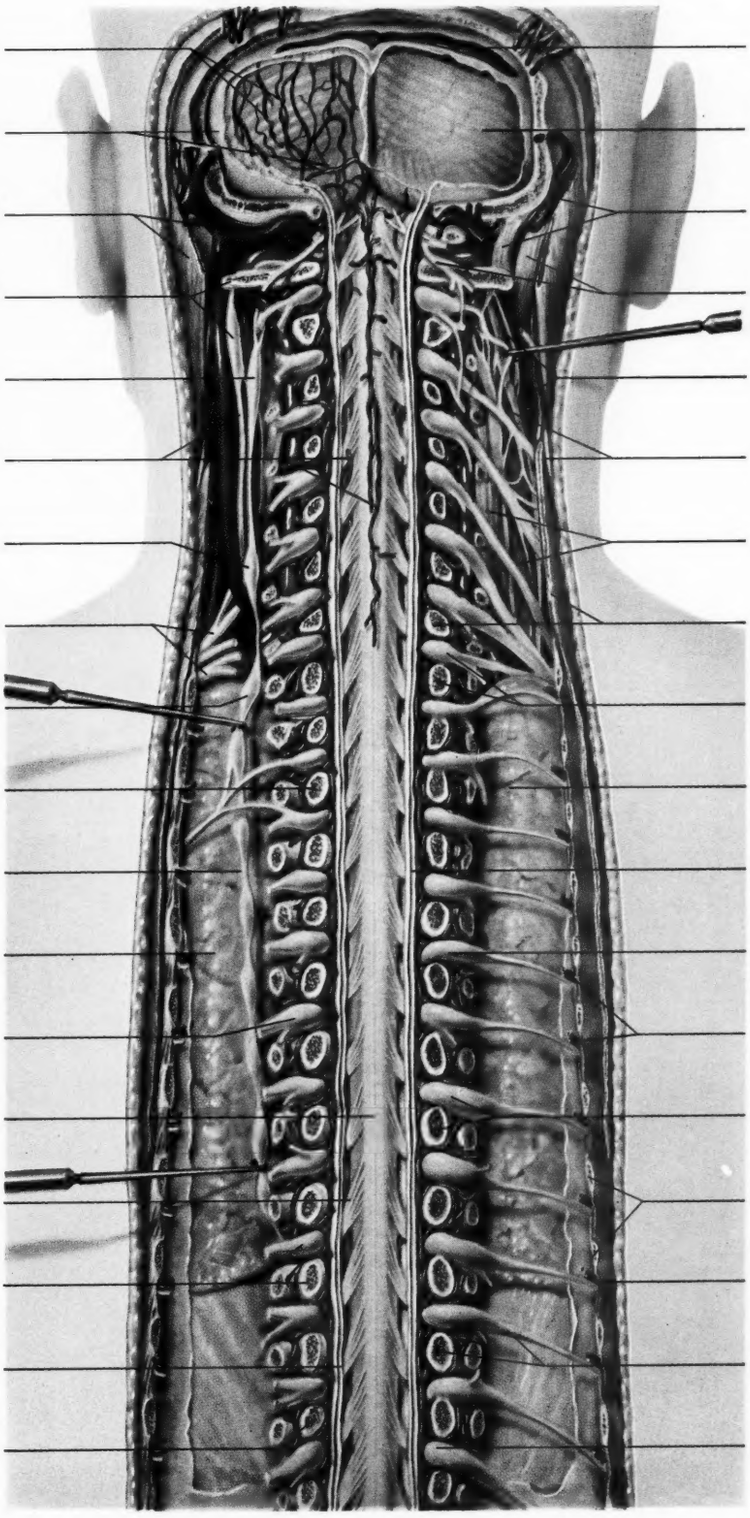
BRAND OF DIBENZYLETHYLENEDIAMINE DIPENICILLIN G

. . . particularly for the treatment of uncomplicated infections due to pneumococci, streptococci, staphylococci and gonococcus as well as other penicillin-sensitive organisms. Supplied in 2 oz. bottles providing 300,000 units DBED penicillin in each peach-flavored teaspoonful.

Pfizer

PFIZER LABORATORIES, BROOKLYN 6, N. Y.,
DIVISION, CHAS. PFIZER & CO., INC.

Cervical *and* Thoracic Regions *of the* Spinal Cord



Inferior cerebellar veins

Cerebral dura (cut); post. inf. cerebellar artery

Sternocleidomastoid muscle; deep cervical vein

Transverse process of atlas; nodose ganglion

Sup. cerv. ganglion

Vagus nerve; post. spinal artery and vein (cut)

Middle cerv. ganglion

Brachial plexus

Inf. cerv. ganglion

Third thoracic vertebra

Sympathetic trunk

Left lung

Sixth thoracic ganglion

Posterior median sulcus

Post. root, ninth thoracic nerve

Ninth thoracic ganglion; tenth thoracic vertebra

Arachnoid (cut)

Twelfth thoracic vertebra

Transverse sinus

Cerebellum (covered by arachnoid)

Rectus capitis lateralis m.; occipital a. and v.

Digastric muscle; first cervical nerve

Hypoglossal nerve; internal jugular vein

Accessory nerve; internal carotid artery

Anterior scalenus muscle; common carotid artery

Seventh cervical vertebra; trapezius muscle

Eighth cervical ganglion; first thoracic vertebra

Right lung

Spinal dura mater (cut)

Fifth thoracic ganglion

Intercostal arteries and veins

Seventh thoracic ganglion; eighth thoracic vertebra

Ribs (cut)

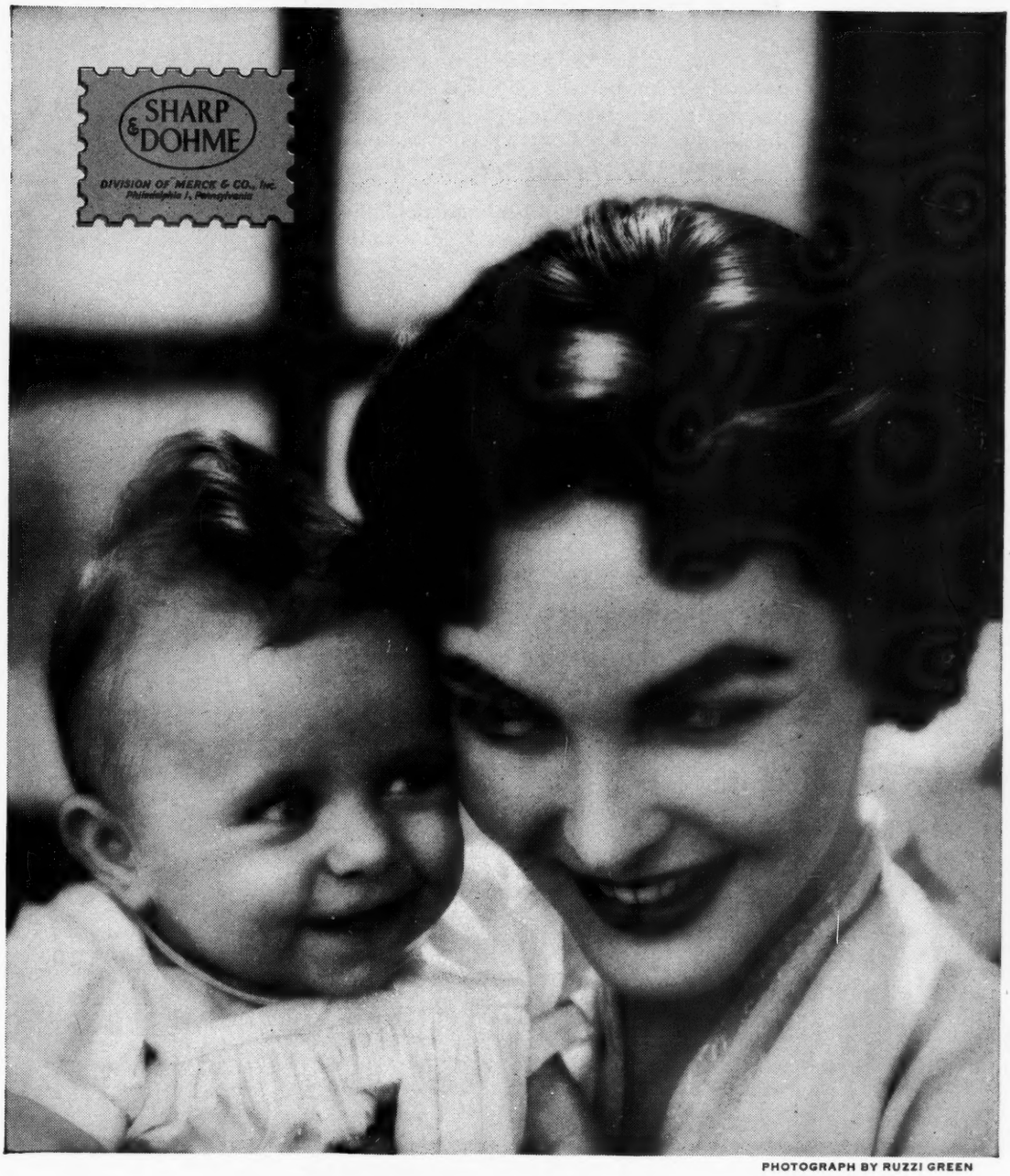
External intercostal muscle

Tenth thoracic nerve; eleventh thoracic vertebra

Twelfth thoracic ganglion

This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle



PHOTOGRAPH BY RUZZI GREEN

For little patients... and big ones, too

PENALEV.

SOLUBLE TABLETS POTASSIUM PENICILLIN G

ACTIONS AND USES: Dissolved in a small amount of liquid, PENALEV Tablets make oral penicillin therapy acceptable to small patients who won't swallow tablets. And they also make penicillin dosage easy to regulate in adult patients. PENALEV Tablets are effective in all infections which may be treated with oral penicillin. Also useful for aerosol therapy and prescription compounding.

DOSAGE: According to the type and severity of the infection.

SUPPLIED: In three dosage strengths—50,000, 100,000 and 250,000 unit tablets in vials of 12 and bottles of 100.

Major advance in dermatitis control:

The new direct approach to the control of dermatitides is hormonal, enlisting the antiphlogistic and antiallergic potency of compound F—foremost of the corticosteroid hormones.

The new objective is adapting corticoid therapy to simple inunction treatment, and obtaining relief in various forms of dermatitides within days —sometimes within hours.

The new attainment is Cortef Acetate Ointment, which rapidly controls edema and erythema, halts cellular infiltration, arrests pruritus in such harassing skin problems as atopic dermatitis, contact dermatitis, pruritus vulvae and ani, neurodermatitis, and seborrheic dermatitis.

Cortef*

Acetate Ointment

Supplied: *Cortef Acetate Ointment is available in 5 Gm. tubes in two strengths—2.5% concentration (25 mg. per Gm.) for initial therapy in more serious cases of dermatitis, and 1.0% concentration (10 mg. per Gm.) for milder cases and for maintenance therapy.*

Administered: *A small amount is rubbed gently into the involved area one to three times a day until definite evidence of improvement is observed. The frequency of application may then be reduced to once a day or less, depending upon the results obtained.*

*TRADEMARK FOR UPJOHN'S BRAND OF HYDROCORTISONE.

A product of Upjohn Research *for medicine...produced with care...designed for health*

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

In Many Respects

THE SAFEST AMONG THE MORE POTENT HYPOTENSIVES

- **lowers blood pressure by centrally induced vasorelaxation**
- **hypotensive action independent of alterations in heart rate**
- **retains its efficacy during prolonged periods**
- **rarely promotes sensitivity or increased tolerance**
- **produces warning symptoms of overdosage before the critical level has been reached**
- **no paralysis of sympathetic activity**
- **no postural hypotension**
- **no compromise of renal function**
- **no reduction in cardiac output or cerebral blood flow**
- **no tachycardia or increase in cardiac work**

These are the desirable pharmacologic and clinical features of Veriloid which establish this alkaloidal extract of Veratrum viride as the safest of the potent hypotensives. Note that your patient need not be hospitalized, can maintain his normal business and social activities, and is not living in constant danger of hypotensive collapse due to sudden changes in posture. No death attributable to Veriloid has ever been reported, yet this drug has enjoyed extensive use during the past five years. Average initial dose, 3 to 4 mg. three times daily after meals, at intervals of not less than four hours.

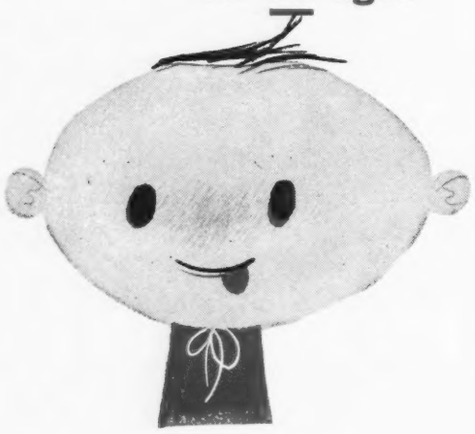
An Original Research Product of

RIKER LABORATORIES, INC.

8480 BEVERLY BLVD., LOS ANGELES 48, CALIF.

VERILOID®

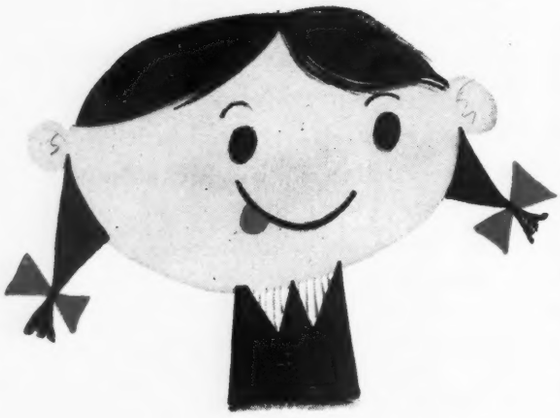
Taste Toppers . . . for all ages



that's what physicians and patients alike call these two favorite dosage forms of Terramycin because of their unsurpassed good taste. They're nonalcoholic — a treat for patients of all ages, with their pleasant raspberry taste. And they're often the dosage forms of first choice for infants, children and adults of all ages.

Terramycin®

BRAND OF OXYTETRACYCLINE



Pediatric Drops

Each cc. contains 100 mg. of pure crystalline Terramycin. Supplied in 10 cc. bottles with special dropper calibrated at 25 mg. and 50 mg. May be administered directly or mixed with nonacidulated foods and liquids. Economical 1.0 gram size often provides the *total dose* required for treatment of infections of average severity in infants.

Supplied: Bottles of 1.0 Gm.

Oral Suspension *(Flavored)*

Each 5 cc. teaspoonful contains 250 mg. of pure crystalline Terramycin. Effective against gram-positive and gram-negative bacteria, including the important coli-aerogenes group, rickettsiae, certain large viruses and protozoa.

Supplied: Bottles of 1.5 Gm.

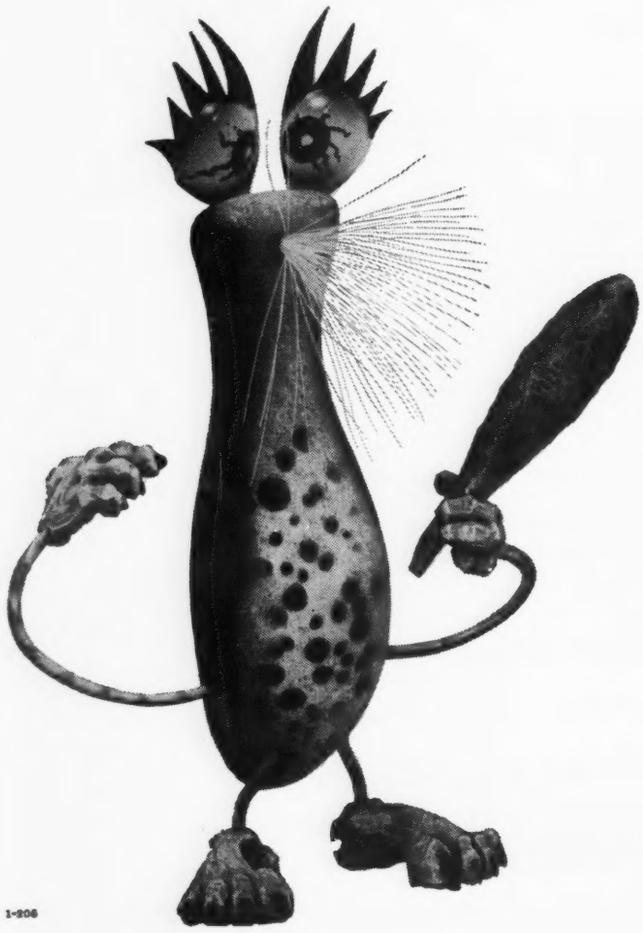
Pfizer PFIZER LABORATORIES, *Brooklyn 6, N. Y., Division, Chas. Pfizer & Co., Inc.*

Against STAPHylococci, STREPtococci and PNEUMOcocci

ALWAYS CONSIDER

*ERYTHROCIN**

a selective antibiotic



1-206

ORALLY EFFECTIVE
against these coccic infections—especially indicated when patients are allergic to penicillin and other antibiotics or when the organism is resistant.

A DRUG OF CHOICE
against staphylococci—because of the high incidence of staphylococci resistant to other antibiotics.

A DRUG OF CHOICE
because it does not materially alter normal intestinal flora; gastrointestinal disturbances rare; no serious side effects reported.

ADVANTAGEOUS
because the special acid-resistant coating developed by Abbott, and Abbott's built-in disintegrator, assure rapid dispersal and absorption in the upper intestinal tract.

USE ERYTHROCIN
in pharyngitis, tonsillitis, scarlet fever, pneumonia, erysipelas, osteomyelitis, pyoderma and other indicated conditions.

Abbott

* Trade Mark
Erythromycin, Abbott
Crystalline

something special in

CORICIDIN

for symptomatic relief

in the common cold

CORICIDIN produces quick suppression of cold symptoms because it contains chlorprophenpyridamine maleate, the most potent antihistamine available. Best results are obtained when CORICIDIN is taken early, but even in later stages considerable comfort is afforded.

CORICIDIN *tablets*

Each CORICIDIN® Tablet contains 2 mg. chlorprophenpyridamine maleate and the standard APC combination.

Schering CORPORATION • BLOOMFIELD, NEW JERSEY

IN CANADA: SCHERING CORPORATION, LTD., MONTREAL

CORICIDIN

The American Journal of Medicine

Vol. XV OCTOBER, 1953 No. 4

Editorial

Exfoliative Cytology of the Digestive Tract

Cells and tissue particles exfoliated by the mucosa of the stomach have been used to diagnose cancer for over half a century. Rosenbach,[1] Ewald,[2] Boas[3] and others[4–6] recorded such diagnoses made by examining sections of tumor particles obtained from lavage or vomitus. Sahli[7] and Elsner[8] were the first to base diagnoses on cytologic criteria in whole unsectioned cells. In Marini's[9] classic investigations, published in 1909, thirty-two of thirty-seven gastric carcinomas were diagnosed by the appearance of unstained cells obtained by meticulous lavage. His excellent morphologic descriptions of the various cell types show clearly that he understood the technical prerequisites for successful gastrointestinal cytodiagnosis. With the advent of radiologic and endoscopic diagnosis, however, cytology was largely forgotten for the next five decades. The revival of the method in recent years has resulted primarily from the work in cervical carcinoma of Papanicolaou[10] and Meigs.[11]

A brief review of the gastrointestinal phase of the field of exfoliative cytology may be helpful. Some recent reports of esophageal,[12] gastric[12–21] and colonic[22] cytology are discouraging in that 50 per cent accuracy is often the best obtainable. It seems that these poor results might have been avoided had Marini's work been remembered, for they are mostly atttributable to digestion of the cells and contamination of the aspirate with food and detritus. Meticulous patient preparation, improved collection methods and increasing cytologic experience minimize but do not obviate these difficulties. Lack of diagnostic cells is to be expected in an intramural lesion or in the occasional advanced ulcerated tumor which is covered by an impenetrable necrotic membrane. An overnight fast is essential prior to examination. If there is any obstruction whatsoever, more vigorous measures are indicated: liquid diet for one to two days prior to examination; lavage until clear with a large lumen tube the night before examination; and overnight continuous suction.

An excellent esophageal specimen may be obtained by simple lavage at the level of the lesion. Adequate gastric specimens are more difficult to obtain because of digestion although

[1] Rosenbach, O. *Deutsche med. Wchnschr.*, 33: 452, 1882.

[2] Ewald, C. A. Klinik der Verdauungskrankheiten, II. Berlin, 1893. August Hirschwald.

[3] Boas, I. Diagnostik und Therapie der Magenkrankheiten. Leipzig, 1896. Georg Thieme.

[4] Rosenheim, T. Krankheiten des Verdauungsapparates. Vienna and Leipzig, 1896. Urban and Schwarzenberg.

[5] Reineboth. *Deutsch. Arch. f. klin. Med.*, 58: 63, 1896.

[6] Cohnheim, P. *Arch. f. Verdauungskrankh.*, 1: 274, 1896.

[7] Sahli, H. Lehrbuch der klinischen Untersuchungsmethoden. Leipzig and Vienna, 1903. F. Deuticke. Cited by Marini.[9]

[8] Elsner, H. *Berl. klin. Jahrb.*, 20: 35, 1908. Cited by Marini.[9]

[9] Marini, G. *Arch. f. Verdauungskrankh.*, 15: 25, 1909.

[10] Papanicolaou, G. N. and Traut, H. F. *Am. J. Obst. & Gynec.*, 42: 193, 1941.

[11] Meigs, J. V., Fremont-Smith, M. and Graham, R. M. *Surg., Gynec. & Obst.*, 77: 449, 1943.

[12] Seybolt, J. F., Papanicolaou, G. N. and Cooper, W. A. *Cancer*, 4: 286, 1951.

[13] Papanicolaou, G. N. and Cooper, W. A. *J. Nat. Cancer Inst.*, 7: 357, 1947.

[14] Frishman, R. L. and Gorin, M. G. *Klin. Med.*, 20: 59, 1942. Cited by Seybolt.[12]

[15] Zimmerman, H. M. and Lubliner, R. *S. Clin. North America*, 29: 501, 1949.

[16] Richardson, H. L., Queen, R. B. and Bishop, F. H. *Am. J. Clin. Path.*, 19: 328, 1949.

[17] Swarts, J. M., Ragins, A. B., Bernstein, A. and Meyer, J. *Gastroenterology*, 14: 265, 1950.

[18] Iverson, K. *Ugesk. f. læger*, 113: 358, 1951.

[19] Porter, J., Spencer, J., Blaisdell, E. R., Appel, J. F. and Herick, S. E. *J. Maine M. A.*, 42: 67, 1951.

[20] Wollum, A., Glaser, D. F., Bryant, H. C. and Pollard, H. M. *J. Nat. Cancer Inst.*, 12: 715, 1952.

[21] Lemon, H. M. *Ann. Int. Med.*, 37: 525, 1952.

[22] Blank, W. A. and Steinberg, A. H. *Am. J. Surg.*, 81: 127, 1951.

Graham[23] reports good results with simple lavage, carefully performed. Panico et al.[24] devised a tube ending in an inflatable balloon covered with a fine netting. This balloon when inflated abrades the gastric mucosa during peristalsis. Excellent sheets of cells are usually obtainable. A constricted gastric antrum may not be abraded. Rubin[25] devised a special abrasive balloon for selected cases, which may be passed into the duodenum with the aid of a distal mercury weight. In the upright position it can be made to ride back and forth between the duodenum and the antrum by inflation and deflation. Rosenthal and Traut[26] developed a method in which the well protected cells contained in the mucous barrier covering the gastric mucosa are released by digesting the mucus with papain. Excellent diagnostic cells may be obtained but the degree of cellular digestion is unpredictable; this interferes with interpretation. Rubin and Benditt[25] have had promising preliminary results with crystalline chymotrypsin in a suitable buffer; the range between mucolysis and cytolysis seems wider than that of papain. Lemon and Byrnes[27] developed duodenal drainage into a valuable diagnostic method for carcinoma of the pancreas and biliary tract. Bader et al.,[28] Wisseman et al.[29] and Rubin[30] have had excellent results in the distal colon using various enema and sigmoidoscopic technics. Attempts[25] are being made to develop methods which will regularly reach more proximal colonic lesions.

Not more than a few minutes should elapse between aspiration and fixation. Packing the aspirate in ice prior to centrifugation slows digestion. All equipment necessary to bring the cells beyond the step of fixation should be available at the bedside. Papanicolaou stain modifications[25,27] have been described which insure good adherence of cells to slides despite the detergent action of bile.

The present status of exfoliative cytology in the diagnosis of gastrointestinal malignancy has been reviewed elsewhere.[31] When cancer is suspected, x-ray complemented by endoscopy usually finds the lesion. The great value of cytodiagnosis is its high accuracy in differentiating the benign from the malignant. McDonald[32] made a cytologic diagnosis of cancer in seventy-five of one hundred proven esophageal malignancies with three false malignant interpretations in benign ulcer of the esophagogastric junction. One investigator[33] diagnosed seven of eight and another[30] six of six proven malignancies; there were no false positives in these two small series. Proven carcinomas have been recorded[33,34] with a negative eosphagoscopic biopsy and positive cytologic study. Cooper[35] and his associates using the abrasive balloon[24] diagnosed thirty-three of forty-five gastric malignancies, an additional seven being suspected. There was only one false diagnosis of cancer in 155 benign stomachs although in eight a suspicion of malignancy was entertained. With papain lavage and other developments, Rosenthal,[36] Imbriglia[33] and Rubin[30] have done equally well. Cytology is especially helpful in differentiating benign from malignant gastric ulcer and gastritis from infiltrative carcinoma. Technical complexities prevent wide use of the method as a screening procedure although selected screening is feasible. In pernicious anemia, gastric ulcer, gastric polyp or the clinical suspicion of carcinoma cytologic examination is considered to be indicated.

By examining the duodenal contents Lemon[21] diagnosed thirteen of thiry-seven primary carcinomas of the pancreas, biliary tract and liver, neoplasm being suspected in an additional ten. There was one false positive in fifty-six benign cases. In a similar series[30] four of seven pancreatic carcinomas were diagnosed; two biliary tract malignancies were missed; there

[23] Graham, R. M., Ulfelder, H. and Green, T. H. *Surg., Gynec. & Obst.*, 86: 257, 1948.

[24] Panico, F. G., Papanicolaou, G. N. and Cooper, W. A. *J. A. M. A.*, 143: 1308, 1950.

[25] Rubin, C. E. *Proc. Cent. Soc. Clin. Res.*, 25: 71, 1952. (To be published in detail elsewhere.)

[26] Rosenthal, M. and Traut, H. F. *Cancer*, 4: 147, 1951.

[27] Lemon, H. M. and Byrnes, W. W. *J. A. M. A.*, 141: 254, 1949.

[28] Bader, G. and Papanicolaou, G. N. *Cancer*, 5: 307, 1952.

[29] Wisseman, C. L., Lemon, H. M. and Lawrence, K. B. *Surg., Gynec. & Obst.*, 89: 24.

[30] Rubin, C. E. *Proc. Damon Runyon Mem. Fund*, October, 1952. (To be published.)

[31] Rubin, C. E., Palmer, W. L. and Kirsner, J. B. *Gastroenterology*, 21: 1, 1952.

[32] McDonald, J. R. *Lancet*, 69: 355, 1949.

[33] Imbriglia, J. E., Stein, G. N. and Lopusniak, M. S. *J. A. M. A.*, 147: 120, 1951.

[34] Anderson, H. A., McDonald, J. R. and Olsen, A. M. *Minnesota Med.*, 32: 1181, 1949.

[35] Cooper, W. A. *J. A. M. A.*, 150: 688, 1952.

[36] Rosenthal, M. *Proc. Second Nat. Cancer Conf.*, March, 1952. (To be published.)

were no false positives in twenty duodenal drainages for benign lesions. It would be desirable to examine all cases of obstructive jaundice early in their course as well as certain patients with undiagnosed upper abdominal symptoms and negative roentgenologic studies.

Wisseman[29] studied cells from 110 colons; of the twenty-eight carcinomas nine were read as positive and seven as suspicious; there was one false positive; all lesions above the sigmoid were missed. Bader[28] in 180 proven cases, including nineteen carcinomas, diagnosed fourteen and suspected four; one cecal carcinoma was diagnosed. There were no false positives but two of the 161 benign cases were falsely suspected of carcinoma. Rubin[30] found cancer cells in nineteen of twenty-three colonic carcinomas including one cecal and one hepatic flexure lesion; there were no false positives. Cytologic study is of special use in differentiating diverticulitis from cancer, benign from malignant polyp and recurrent malignancy from operative stricture. Cell study is also indicated if the source of occult blood cannot be found.

Gastrointestinal cell study is an excellent tool for clinical investigation. Over the years, repeated harmless cell samplings can be taken from the lumen of organs prediposed to cancer such as the stomach in pernicious anemia, achlorhydria or polyposis and the colon in long-standing ulcerative colitis or polyposis. Organs which have been partially resected for cancer bear repeated study. Much might be learned concerning the genesis of carcinoma. Gastroscopic biopsy will undoubtedly help to correlate tissue morphology with the cell types seen in the cytologic preparation.

Although cytologic material lacks the architectural pattern of tissue sections, it has many advantages for basic study. Living, three dimensional cells may be investigated with the newer physical and chemical technics.[37] Fine cell detail can be examined by phase microscopy without introducing staining and sectioning artefacts. The electron microscope cannot be used to study submicroscopic structure in living cells since fixed sections of 0.1 μ thickness are necessary. Moon[38] has devised an ingenious x-ray apparatus which may be adapted to microscopy of the living cell at magnifications ten to a hundred times that of the optical microscope. The resolution will be limited only by the wave length of the soft x-ray used. The cell will be scanned by a pin-point x-ray source and thus injurious exposure will be avoided.[39] Cells may be investigated by differential centrifugation so that various cellular elements can be separated in sufficient quantity for chemical analysis. Tissue culture offers a biologic approach to this material. Enzyme stains may give useful information about cell origin and function. Freeze-dry fixation may eliminate certain fixation artefacts. Many other basic approaches are available.

When properly performed, study of the exfoliated cells in various parts of the digestive tract is a valuable complement to the other diagnostic methods. For the present it is most applicable to selected case material. The extent of its future application as a general screening method depends on simplification of technics and wider training in their application. The procedure may prove very useful in basic biologic and clinical investigation. It is to be hoped that this field will be subjected to thorough, objective investigation unmarred by the overenthusiasm of its protagonists or the cynical scepticism of the critics. There is much to learn.

WALTER L. PALMER, M.D.
CYRUS E. RUBIN, M.D.
Department of Medicine,
University of Chicago,
Chicago, Illinois

[37] BOURNE, G. H. Cytology and Cell Physiology. London, 1951, Geoffrey Cumberlege.

[38] MOON, R. J. *Science*, 112: 389, 1950.

[39] Personal communication.

Clinical Studies

Genetic and Biochemical Aspects of Wilson's Disease*

A. G. Bearn, M.D. (London)
New York, New York

In 1912 Kinnear Wilson published his classical monograph on "progressive lenticular degeneration.[1] He described thirteen cases of which eight were familial and concluded that the condition was "very often familial but was not congenital or hereditary." Since Wilson's paper there have been remarkably few large series of cases of Wilson's disease reported and its genetic aspects have received scant attention. It is usual to regard the condition as inherited in a recessive manner. This concept, however, has not been universally accepted. "Its familial character might equally well be due to the exposure of members of a family to the same environment as to their participation in a common inheritance."[2] Hall[3] in 1921 was the first to review the literature after Kinnear Wilson's monograph. He described seven additional cases and considered that the condition was probably recessive but was puzzled by the lack of consanguinity in the parents of his cases. Moreover, it was his opinion that there were probably two genes considered with the inheritance, both of which were necessary before the disease became manifest. Later Kehrer,[4] Stadler,[5] André and van Bogaert,[6] Dent and Harris,[7] and Matthews et al.[8] brought forward evidence that the disease is inherited in a recessive manner. These authors, however, obtained their material primarily from previously recorded cases in the literature, a method which is inevitably liable to error if insufficient details have been recorded.

GENETIC FINDINGS

The collection of fourteen propositi who suffered from Wilson's disease has enabled a reinvestigation of the genetic aspects of the disease to be undertaken, as well as an investigation of its biochemical abnormalities. The details of the latter will form the basis of a separate report. A total of twenty-six cases of Wilson's disease were revealed in the sixteen families studied. In no case were either of the parents of the affected individuals found to be suffering from overt Wilson's disease nor, in the cases available for detailed study, was any biochemical abnormality suggestive of Wilson's disease detected. The simplest genetic explanation for these observations is that the condition is recessively inherited and the affected individuals inherit a genetic contribution from both parents who, while phenotypically normal, are heterozygous for the abnormal allele. Homozygosis is more likely to occur in the offspring of marriages between close relatives than from marriages between genetically non-related persons. If the allele responsible for Wilson's disease is recessive, it is clearly of particular importance to estimate the incidence of consanguinity in the affected families. If an individual is heterozygous for a certain abnormal allele, the chance of meeting the same allele in a random marriage is simply the gene frequency for the allele concerned. However, should union occur with a related person the probability of meeting the abnormal allele is considerably increased. When an individual is heterozygous for such an allele, the probability of a first cousin having the same allele is one in eight, and hence the chance of such a union producing a homozygous affected person is one in thirty-two.

The incidence of first cousin marriages in the parents of sixteen patients with Wilson's disease occurring in separate families was 37.5 per cent. The actual consanguinity rate was even higher since, in our data, marriage between second cousins occurred three times and the parents of one patient were half first cousins once removed, giving a total consanguinity rate of 62.5 per cent. Illustrative pedigrees are shown in Figures 1 to

* From the Hospital of The Rockefeller Institute for Medical Research, New York, N. Y.

4. The incidence of first cousin marriages is higher than is usually recorded for recessively inherited conditions. A high incidence of cousin marriages should occasionally reveal other rare recessive abnormalities. If this occurs it may be possible to estimate the probability of the two genes being situated on the same or on different chromosome pairs.[9] If an individual is heterozygous for two recessive traits, the probability of a first cousin carrying both those traits is 1:64. This may have occurred in the parents of the propositus T. M. (Fig. 4) in whom examination also revealed retinitis pigmentosa without complicating deafness. A consideration of this pedigree, however, does not suggest any close genetic linkage.

Sex Ratio. The sex incidence of Wilson's disease is uncertain, although the disease is often considered to occur more commonly in males. In this small series of twenty-six cases (twenty-five zygotes, since this number includes one pair of uniovular female twins) a 1:1 sex ratio was not observed, as seventeen males and eight females were found. This deviation from equality is probably significant, p = .0322. It is of interest that of the eight female cases three came from

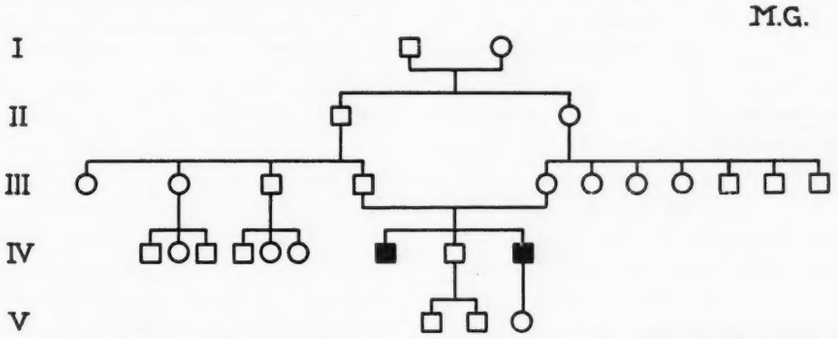


FIG. 1. Pedigree of affected siblings whose parents were first cousins. The single offspring of affected individual is clinically and biochemically normal (age six years).

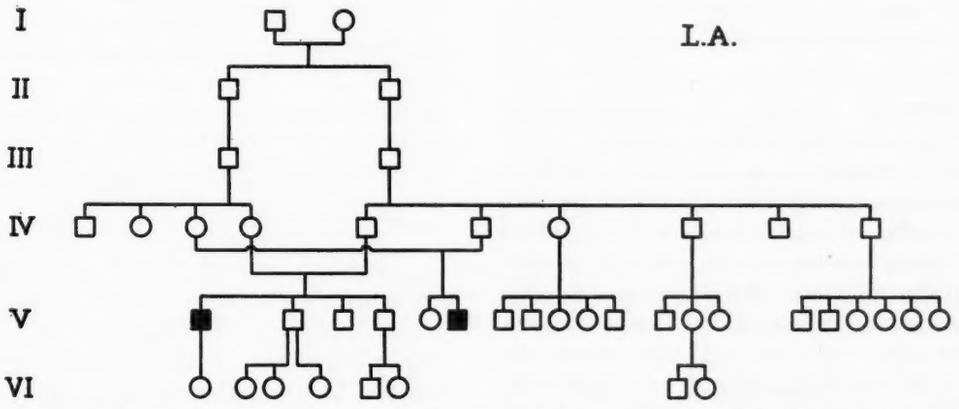


FIG. 2. Pedigree showing two instances of second cousin marriages, each having an affected offspring.

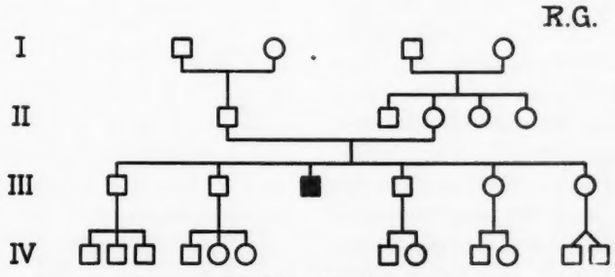


FIG. 3. Pedigree of affected sibling with unrelated parents.

one family (Y. R.) in which there was also an unusually large number of affected individuals. If this family had not been observed, there would have been an undoubted male predominance in the calculated sex ratio.

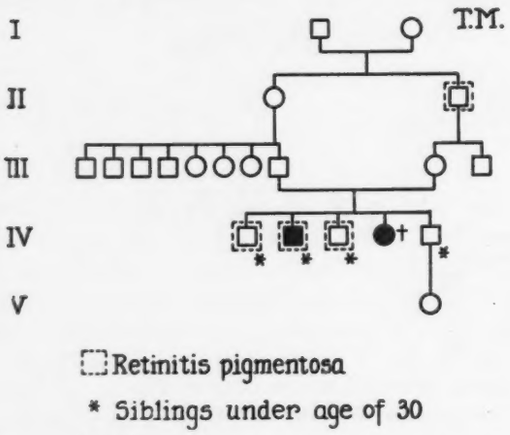


FIG. 4. Pedigree illustrating the occurrence of Wilson's disease and retinitis pigmentosa in same family; first cousin consanguinity present in the parents.

The evidence brought forward thus far strongly suggests that Wilson's disease is inherited in a recessive manner. As a corollary it is clear, from consideration of simple mendelian laws, that the marriage of an affected individual to a genetically non-related person will produce affected offspring only if that person is also heterozygous for the abnormal gene. This will clearly be very unlikely and will depend upon the frequency of the abnormal gene in the general population. Two affected individuals, M. G. and L. A., are married to genetically non-related persons and in none of their progeny so far have clinical or biochemical stigmas of Wilson's disease developed.

Genetic Ratio. The fitting of the data to a mendelian ratio is probably the most secure basis for any genetic hypothesis.[10] Proof of a 1:3 ratio, which would be expected if the recessive hypothesis is correct, must take into account the small size of families upon which the calculations are based. The *a priori* method for calculating genetic ratios has been elaborated by Bernstein[11] and is designed to correct this source of error and enable a genetic ratio to be calculated with more accuracy. (Table I.) In our series of cases in 80 per cent signs or symptoms of the disease had developed before the age of thirty and therefore unaffected siblings who have not yet reached the age of thirty or who died before reaching this age have been excluded (eleven females and twelve males). The total number of affected individuals is twenty-six (twenty-five zygotes) and the total number of siblings will become fifty-nine. (Table II.)

TABLE I
EXPECTED AND OBSERVED NUMBER OF CASES OF WILSON'S DISEASE IN FAMILIES OF VARYING SIZE

Size of Family	No. of Families	q'n*	Cases Expected	Cases Observed
1	3	1.0	3.0	3
2	4	1.143	4.57	5
3	3	1.297	3.89	6
4	1	1.463	1.46	1
6	4	1.825	7.34	8
10	1	2.515	2.51	2
	16		22.77	25

* Factor $q'n = \frac{1/4^n}{1 - (3/4)^n}$

Number of families × Factor = cases expected

TABLE II
SUMMARY OF THE GENETIC DATA IN THE FAMILIES STUDIED

Case	No. of Affected Siblings			Total No. of Siblings†			Parental Consanguinity	
	M	F	Total	M	F	Total	1st Cousin	2nd Cousin
1, R. G.	1	0	1	4(4)	2(2)	6	0	0
2, G. V.	1	1	2	3(5)	7(8)	10	1	0
3, M. G.	2	0	2	3(3)	0(0)	3	1	0
4, C. P.	1	0	1	1(1)	1(1)	2	0	0
5, J. M.	1	0	1	1(2)	2(2)	3	1	0
6, W. C.	2	0	2	6(6)	0(2)	6	1‡	0
7, L. A.	1	0	1	4(4)	0(0)	4	0	1
8, A. A.	1	0	1	1(1)	1(1)	2	0	1
9, C. R.	2	1	3	2(2)	1(2)	3	0	1
10, P. C.	0	1	1	1(1)	1(3)	2	1	0
11, S. B.	1	0	1	0(1)	1(1)	1	0	0
12, T. M.	1	1	2	1(3)	1(2)	2	1	0
13, Y. R.	1	4*	5	2(2)	5(5)	7	1	0
14, M. F.	1	0	1	3(3)	3(3)	6	0	0
15, J. B.	1	0	1	1(3)	0(1)	1	0	0
16, S. S.	0	1	1	0(4)	1(4)	1	0	0
Total	17	9	26	33	26	59	6	3

* Includes one pair of uniovular twins

† Numbers in parentheses are total siblings including those under the age of thirty or who died before this age

‡ Half first cousin once removed

The expected genetic ratio, if Wilson's disease is inherited in a recessive manner, is 1:1.58, whereas a ratio of 1:1.36 was observed. Two more affected siblings were found than were anticipated from theoretic considerations. This difference is not statistically significant. ($X^2 = 0.284$ and $p > .5$)

Recently Matthews and his associates,[8] using the same method, investigated the mode of inheritance of Wilson's disease by reviewing the past literature. Although their results were similar, they were unable to obtain a ratio which fitted the recessive hypothesis. As suggested by these authors this was probably due to the biased nature of the data upon which the calculations were made. Their experience emphasizes the difficulty of applying such calculations when pedigrees are recorded in insufficient detail.

Gene Frequency. The estimation of the frequency of an abnormal allele is inexact and it is rare that dogmatic assertions can be validated. Nevertheless some approximations are possible. By applying Dahlberg's formula it can be deduced, as an approximation, if one assumes panmixia, that $p = \frac{a(1 - x)}{16x}$ where p = gene frequency, a = frequency of cousin marriages in the general population, and x = observed incidence of cousin marriages in the genetic material to be analyzed. One of the many limitations of this calculation is the error introduced in the figure chosen for the incidence of cousin marriages in the general population. Julia Bell in England found a frequency of 0.61 per cent in a "general hospital population." Other estimates are higher and reach maximum values in small isolates in which the consanguinity rate may reach 10 per cent. The probable range, however, is between 0.5 and 1.0 per cent. Using the consanguinity rate of 0.5 per cent in the foregoing formula

$$p = \frac{.005(1 - 0.375)}{16 \times 0.375} = .000521$$

The gene frequency is roughly 1 in 2,000 and the expected disease incidence 1 in 4 million. An assumed 1 per cent consanguinity rate, which is almost certainly far too high, gives rise to a gene frequency of 1 in 1,000 and an expected disease incidence of 1 in a million. The population of greater New York, the area from which the cases have been largely drawn, is approximately 8 million. Thus, depending on the figure chosen for (a), two or eight cases of Wilson's disease should be present in the greater New York area. We have collected sixteen cases of Wilson's disease and it is clearly absurd to suppose that we have collected all the cases from this area. These facts strongly suggest that our data are not representative of the general population and that we are dealing with isolates which have a high incidence of consanguinity, the gene frequency being higher in these isolates than in the general population. These theoretic considerations are supported by examining the racial characteristics of the present material, 31 per cent of whom are Italian and 50 per cent Jewish, groups usually considered to have a high coefficient of inbreeding. It is possible that the abnormal genes occurring in these two groups arose from separate mutations.

BIOCHEMICAL FINDINGS

In his original monograph Kinnear Wilson suggested that the etiology of the disease might be due to the effect of an undetected toxin. There are many references in the German literature indicating the possible relationship of metallic intoxications to this disease. Copper, silver and manganese have been implicated by various authors, and this literature has been recently summarized by Denny-Brown and Porter,[12] and Matthews and co-workers.[8]

Reawakening of interest in this disease followed the report by Glazebrook[13] of a patient with Wilson's disease whose liver and brain at autopsy revealed a high copper content. Three years later Mandelbrote et al.[14] made the important chance observation that a patient suffering from Wilson's disease excreted an increased amount of copper in the urine. In the same year Uzman and Denny-Brown[15] demonstrated an increased excretion of aminoacids in patients with Wilson's disease and, in a later paper, Porter[16] confirmed the original finding of Mandelbrote. Although Denny-Brown and Porter[12] did not report any observations on serum copper in their patients, they suggested at that time that the serum copper was probably raised and overflowed into the urine due to a low renal threshold. Cooper et al.[17] did not find an elevated plasma aminoacid level in patients with Wilson's disease, and regarded the aminoaciduria as evidence of a defect in the renal reabsorption of aminoacids by the tubules.

The collection of blood from nine cases of Wilson's disease enabled a re-evaluation of the serum copper level in this disease to be undertaken. Serum copper was estimated (using 5 ml. samples) according to the method of Eden and Green.[18] In eight of nine cases the serum copper was found to be considerably lower than

normal.[19] Since the original report blood from a further eight cases of Wilson's disease has been studied and in a total of seventeen cases the serum copper concentration is lower than normal in fifteen. (Fig. 5.) In the remaining cases the serum copper concentration was found to be in the low normal range.

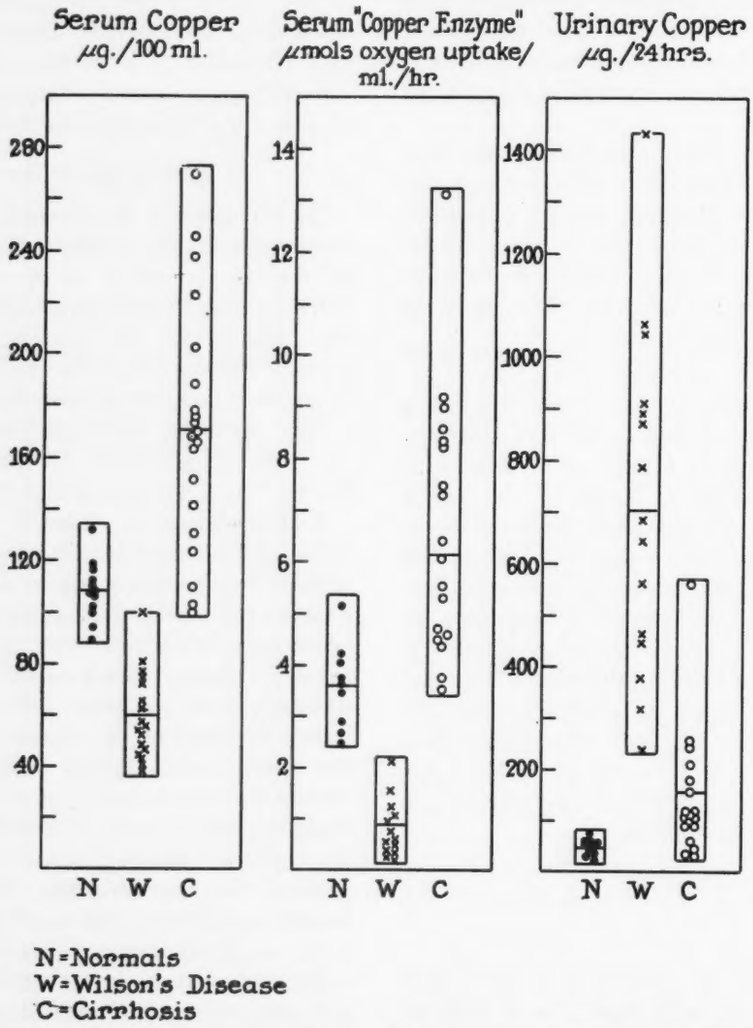


FIG. 5. Comparison of amounts of serum copper, serum "copper enzyme" and urinary copper in normal subjects, cirrhotic patients and patients with Wilson's disease. Horizontal lines represent mean values.

Copper is known to be the prosthetic group of many enzymes and Holmburg and Laurell[20–22] have shown that copper in the serum exists as a firmly bound metalloprotein (coeruloplasmin) which can be shown to exhibit oxidase activity and furthermore that a direct relationship normally exists between the serum copper and the serum copper oxidase activity. Since other recessively transmitted conditions such as cystinuria, alkaptonuria and phenylketonuria have been explained on the basis of a disordered enzyme system, the serum copper oxidase activity was measured in patients suffering from Wilson's disease and was found to be conspicuously lower than normal.[19] Further observations support these findings. Serum copper oxidase activity has now been studied in thirteen patients with Wilson's disease. In all cases there has been a marked and consistent reduction in oxidase activity. (Fig. 5.) It was of interest that in patients who were found to have a serum copper level in the low normal range the serum oxidase activity was lower than normal. It is certainly possible that coeruloplasmin in the intact organism does not have an enzymatic function and it must also be conceded that if it is an enzyme its normal substrate is, at present,

quite unknown. Recently Scheinberg and Gitlin[23] have produced further evidence that coeruloplasmin is deficient in Wilson's disease. Using spectrophotometric and immunochemical technics they also demonstrated a low coeruloplasmin level in patients with Wilson's disease.

Twenty patients suffering from various types of cirrhosis were examined and serum copper analyses carried out. The serum copper level was found to be usually elevated, and in no case was a lowered serum copper level found. The serum copper level in cirrhosis, however, was found to be extremely variable, depending in large part upon the type of cirrhosis concerned. Patients with Laennec's cirrhosis did not have a greatly elevated serum copper level, while patients with biliary cirrhosis were found to have an extremely high serum copper concentration (data to be published), a finding which is in accord with the belief of van Ravesteyn[24] that in normal individuals copper is excreted in the bile.

The high urinary excretion of copper in Wilson's disease was confirmed in our cases. (Fig. 5.) Urinary copper was estimated using a modification of the method of Eden and Green.[18] An increased excretion of copper following the administration of BAL was invariably found. A similar increase in the excretion of copper following the administration of a chelating agent, versene®* (calcium disodium versenate), was also noted. The high urinary excretion of copper is not alone diagnostic of Wilson's disease since many patients with cirrhosis excrete an increased amount of urinary copper and, particularly in long-standing cases of biliary cirrhosis, the urinary excretion of copper may occasionally be in the range commonly found in patients suffering from Wilson's disease. A low serum copper associated with a high urinary excretion of copper is, however, of considerable diagnostic importance in Wilson's disease. The characteristic biochemical abnormalities occur whether the disease exhibits predominantly neurologic or hepatic symptomatology and has been found in a patient who has no neurologic signs or symptoms and who had previously been thought to be suffering from juvenile cirrhosis of unknown etiology (data to be published).

The finding of an abnormal aminoaciduria, first reported by Uzman and Denny-Brown,[15] has also been noted in our patients. The urinary aminoacid abnormality in this disease has been greatly clarified by the work of Moore and Stein[25] on urine collected from six of our cases. Using ion exchange columns they have demonstrated a considerable increase (five to twenty-fold) in the excretion of many of the aminoacids found in normal urine. However, taurine, aspartic acid, isoleucine, methyl histidine and arginine were excreted in amounts close to the normal range. In addition, proline and citrulline, two aminoacids not found in normal urine,[26] were frequently present. The relationship between urinary copper excretion and aminoaciduria has already been emphasized.[19]

Any unifying concept of Wilson's disease must explain the paradoxic finding of an increased excretion of copper in the urine and a lowered serum copper (coeruloplasmin) level and also explain the aminoaciduria which is found though the total plasma aminoacids are not significantly elevated.

There is little doubt that patients with Wilson's disease absorb more dietary copper than normal individuals and hence a comparison has been made between Wilson's disease and hemochromatosis.[12] The serum iron is elevated in hemochromatosis while in Wilson's disease the serum copper is conspicuously decreased. The renal tubular defect postulated by Cooper et al.[17] to account for the increased aminoacid excretion in the urine has also been found by Matthews et al.[8] While a tubular defect probably exists, it cannot alone explain the high tissue copper and the low serum copper.

Scheinberg and Gitlin[23] have recently suggested that Wilson's disease is an example of disease caused by a deficiency of a specific plasma protein. An increased absorption of copper by the gut in Wilson's disease may not be a primary defect but a consequence of the low coeruloplasmin level. The excess copper absorbed is then deposited in the tissues. The amount deposited in any particular tissue is, in large part, an expression of the capacity of that particular tissue to bind copper. The form in which that binding takes place is not yet well understood. The copper is probably either firmly attached to a protein or more loosely bound to aminoacids or peptides. The improvement in the neurologic signs and symptoms which followed the administration of chelating agents such as BAL and versene suggests that in the brain the excess copper is loosely bound

* The versene used was kindly supplied by Riker Laboratories, Inc., Los Angeles, Calif.

and the tissue affinity is easily overcome by the chelating agent. The lack of improvement in hepatic function following the administration of these agents suggests that the excess copper in the liver is more tightly bound and the tissue affinity is less easily overcome by the chelating agents so far employed. In the urine it seems probable that copper is excreted bound, at least in part, to aminoacids. This is emphasized by the finding of a direct correlation between urinary copper excretion and urinary aminoacid excretion in patients with Wilson's disease.[19] Further confirmatory evidence of the importance of this relationship comes from the observation that elevation of the urinary excretion of aminoacids results in a prompt increase in the urinary excretion of copper.[8] These findings have been confirmed. Extended metabolic studies suggest that this response is not restricted to acute experiments and thus increasing the urinary excretion of aminoacids provides a method for increasing the excretion of copper over a prolonged period of time.[27]

CONCLUSIONS

1. Twenty-six cases of Wilson's disease have been revealed in sixteen families. A first cousin consanguinity rate of 37.5 per cent has been demonstrated.

2. Examination of the pedigrees suggests that the disease is inherited in an autosomal recessive manner. Calculation of the genetic ratio strongly supports this hypothesis.

3. Biochemical studies confirm a high urinary excretion of aminoacids and copper in Wilson's disease. In some other types of liver disease the urinary excretion of copper was also increased.

4. A low serum copper was observed in fifteen of seventeen cases of Wilson's disease studied. In all cases a low serum "copper enzyme" (coeruloplasmin) level was demonstrated. These findings appear to be characteristic of Wilson's disease and were not found in patients with other forms of liver disease, in whom the serum copper and serum "copper enzyme" levels were frequently elevated.

5. Whether the specific inherited metabolic abnormality in Wilson's disease is primarily associated with an abnormal copper or an abnormal aminoacid metabolism is not clear. The establishment of the recessive mode of inheritance would support either hypothesis.

Acknowledgment: I am very much indebted for constant help and advice to Dr. Henry G. Kunkel, in whose department this work was carried out. I am also grateful to Dr. William H. Stein and Dr. Stanford Moore for their help in certain aspects of this work and to Dr. L. C. Dunn and Dr. Donald Lancefield for genetic advice.

The collection of these cases of Wilson's disease was made possible only through the kind generosity of many New York neurologists, particularly Dr. Houston Merritt, Dr. Harold Wolff and Dr. Theodore Von Storch. The skilled technical assistance of Mr. Charles Galati was much appreciated.

REFERENCES

1. Wilson, S. A. K. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain*, 34: 295, 1912.
2. Brain, W. R. Diseases of the Nervous System, 4th ed., p. 550. London, 1951.
3. Hall, H. C. La Dégénérescence hépato-lenticulaire. Paris, 1921.
4. Kehrer, F. Zur Ätiologie und Nosologie der Pseudosklerose Westphal-Wilson. *Ztschr. f. d. ges. Neurol. u. Psehiat.*, 129: 488, 1930.
5. Stadler, H. Die Erkrankungen der Westphal-Wilsonchen Pseudo-sklerose auf Grund anatomischer, klinischer und erbbiologischer Untersuchungen. *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 164: 583, 1939.
6. André, M. J. and van Bogaert, L. L'hérédité dans la dégénérescence hépató-lenticulaire et le problème des rapports intrinsèques de la pseudosclérose de Westphal-Strümpell et de la maladie de Wilson. *Encéphale*, 39: 1, 1950.
7. Dent, C. E. and Harris, H. The genetics of cysturia. *Ann. Eugenics*, 16: 60, 1951.
8. Matthews, W. B., Milne, M. D. and Bell, M. The metabolic disorder in hepato-lenticular degeneration. *Quart. J. Med.*, 84: 425, 1952.
9. Roberts, J. A. F. Genetic linkage in man, with particular reference to usefulness of very small bodies of data. *Quart. J. Med.*, 14: 27, 1945.
10. Roberts, J. A. F. An Introduction to Medical Genetics. London, 1940. Oxford University Press.
11. Bernstein, F. Variations- und Erblichkeitsstatistik. Berlin, 1929. Gebrüder Borntraeger.
12. Denny-Brown, D. and Porter, H. The effect of B.A.L. (2,3 dimercaptopropanol) on hepatolenticular degeneration (Wilson's disease). *New England J. Med.*, 245: 917, 1951.
13. Glazebrook, A. J. Wilson's disease. *Edinburgh M. J.*, 52: 83, 1945.
14. Mandelbrote, B. M., Stanier, M. W., Thompson, R. H. S. and Thruston, M. N. Studies on copper metabolism in demyelinating diseases of central nervous system. *Brain*, 71: 212, 1948.
15. Uzman, L., and Denny-Brown, D. Aminoaciduria in hepatolenticular degeneration (Wilson's disease). *Am. J. M. Sc.* 215: 599, 1948.
16. Porter, H. Amino acid excretion in degenerative

diseases of nervous system. *J. Lab. & Clin. Med.*, 34: 1623, 1949.

17. Cooper, A. M., Eckhardt, R. D., Faloon, W. W. and Davidson, C. S. Investigation of aminoaciduria in Wilson's disease (hepatolenticular degeneration): demonstration of defect in renal function. *J. Clin. Investigation*, 29: 265, 1950.
18. Eden, A. and Green, H. H. Micro determination of copper in biological material. *Biochem. J.*, 34: 1202, 1940.
19. Bearn, A. G. and Kunkel, H. G. Biochemical abnormalities in Wilson's disease. *J. Clin. Investigation*, 31: 616, 1952.
20. Holmberg, C. G. and Laurell, C. B. Investigations of serum copper. I. Nature of serum copper and its relation to the iron binding protein in human serum. *Acta chem. Scandinav.*, 1: 944, 1947.
21. Holmberg, C. G. and Laurell, C. B. Investigations in serum copper. II. Isolation of the copper containing protein and a description of some of its properties. *Ibid.*, 2: 550, 1948.
22. Holmberg, C. G. and Laurell, C. B. Investigations in serum copper. III. Coeruloplasmin as an enzyme. *Ibid.*, 5: 476, 1951.
23. Scheinberg, I. H. and Gitlin, D. Deficiency of coeruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). *Science*, 116: 484, 1952.
24. van Ravesteyn, A. H. Metabolism of copper in man. *Acta med. Scandinav.*, 118: 163, 1944.
25. Moore, S. and Stein, W. H. Aminoaciduria in Wilson's disease. Proc. 2nd Internat. Cong. Biochem., p. 367. Paris, 1952.
26. Stein, W. H. A chromatographic investigation of the amino acid constituents of normal urine. *J. Biol. Chem.*, 201: 45, 1953.
27. Bearn, A. G. and Kunkel, H. G. Data to be published.

Liver Dysfunction in Hepatolenticular Degeneration*

A Review of Eleven Cases

EDWARD C. FRANKLIN, M.D. *and* ARTHUR BAUMAN, M.D.
New York, New York

HEPATOLENTICULAR degeneration (Wilson's disease) consists of a combination of extrapyramidal and hepatic disease, in association with a ring of pigment at the corneal margin known as the "Kayser-Fleischer ring." In his classical description Wilson[1] pointed out that advanced cirrhosis of the liver is a constant finding at necropsy. On the other hand, he emphasized the paucity of signs and symptoms of hepatic dysfunction during life. In a later report[2] he stated that jaundice and ascites may precede the neurologic symptoms and that there may be terminal hematemesis but that "the customary symptoms and signs of cirrhosis very seldom indeed occur."

Although there have been several reports on Wilson's disease in which clinical evidence of liver dysfunction was obvious,[3–8] many authors still underemphasize its clinical importance. The purpose of this report is to point out the frequency and severity of signs and symptoms of hepatic dysfunction in Wilson's disease. This opinion is based on a review of eleven cases of hepatolenticular degeneration studied at the Montefiore Hospital during the past seventeen years.

MATERIAL AND METHODS

Twelve patients with hepatolenticular degeneration have been observed at the Montefiore Hospital since 1934. One case is not included in the present report because the patient was observed for only five days. In the others evidence of hepatic damage was determined from the clinical and laboratory data and, when available, from the results of postmortem examination.

CASE REPORTS

CASE 1. B. H., a sixteen year old girl, was first admitted to the Montefiore Hospital in 1934 because of dysarthria of two years' duration. The patient's twin sister is reported as Case 10. Their parents were first cousins. At the age of ten years the patient had an episode of vomiting and ascites. Exploratory laparotomy was performed and a diagnosis of cirrhosis of the liver was made. Subsequently multiple paracenteses were performed. Two years later her speech became dysarthric and her family noted a change in facies and gait.

On physical examination the spleen was palpable 2 cm. below the costal margin. Kayser-Fleischer rings were present bilaterally. There was a vacuous facial expression, her mouth was open and her smile silly. There was flattening of the left side of the face. Ataxia, tremor, "wing beating," dysarthria, rigidity, hyperreflexia and dysdiadochokinesis were present.

Following hospital discharge in 1935 the patient was seen in the clinic from 1935 to 1940. There was slow progression of neurologic symptoms. When she was readmitted in 1940, she lay helplessly in bed with her head tilted to the right. The sensorium was dulled. She had frequent convulsive seizures without loss of consciousness. Twenty-four hours after admission the patient had a massive hematemesis and became comatose. Repeated hematemeses occurred. She became febrile and died in June, 1940, twelve years after the onset of her illness. During the period that this patient was observed tests of liver function indicated progressive impairment. (Table 1.)

Postmortem examination showed the following significant findings: The liver weighed 650 gm.; it was firm and nodular. The findings were characteristic of multilobular cirrhosis. The spleen weighed 390 gm. There was dilation and tortuosity of the esophageal veins. The lungs

* From the Division of Neuropsychiatry of the Montefiore Hospital, New York, N. Y.

showed extensive bronchopneumonia. The findings in the brain were similar to those usually seen in Wilson's disease.

CASE 2. F. K., a thirty-five year old white female, was first admitted to the Montefiore Hospital in 1945 because of involuntary movements of all extremities of three years' duration. Seven years before admission splenomegaly was noted during an otherwise normal pregnancy. During the same year she had gastrointestinal disturbances and was treated with an ulcer regimen. Five years before admission she developed ascites without jaundice. A year later she had toxemia of pregnancy. Subsequently a tubal ligation was performed during which "lobular cirrhosis" of the liver was noted. Three years before admission a tremor of the right arm appeared which gradually involved all four extremities. At first the tremor was present only during activity but later it was also noted at rest. Shortly thereafter her speech became slow and irregular. At the time of admission the patient was unable to walk or care for herself.

Physical examination revealed an obese white female. The liver was felt 2 cm. below the costal margin. The spleen reached the iliac crest. Kayser-Fleischer rings were present bilaterally. Examination revealed a euphoric, bedridden female with a smiling, open-mouthed facies. She could not feed herself. There was a coarse alternating tremor of the head and extremities, "wing beating," hypertonicity of all extremities, weakness of the lower extremities, absent abdominal skin reflexes, right ankle clonus and a right Babinski sign.

During her hospital stay the disease progressed slowly. In 1947 she became depressed and, following several attempts at suicide, she was transferred to a psychiatric institution where she continued to be restless, resistive, uncooperative, depressed and showed defects in her sensorium. Her physical status deteriorated rapidly. A few months later she died of bronchopneumonia, nine years after the onset of her illness. During her last three years of life hepatic function was markedly impaired as shown by liver function tests. (Table 1.)

Necropsy at another hospital revealed a small,

TABLE 1

TESTS FOR HEPATIC FUNCTION IN WILSON'S DISEASE

Case	Date	Cephalin Flocculation	Thymol Turbidity U	Total Serum Protein (gm./100 cc.)	Serum Albumin (gm./100 cc.)	Serum Globulin (gm./100 cc.)	Bromsulfalein Retention		Alkaline Phosphatase, Bodansky units	Prothrombin Time—sec.		Blood Cholesterol (mg./100 cc.)	Cholesterol Esters (mg./100 cc.)	Serum Bilirubin (direct) (mg./100 cc.)	Icterus Index U
							% in 30 min.	% in 45 Min.		Whole	1:8 Diluted				
Patients with Clinical Signs of Hepatic Dysfunction															
1. B. H.	1934	....	....	6.5	4.7	1.8	5	..	....	....	....	140	123	....	7
	1940	....	....	4.7	2.8	1.9	60	..	....	....	....	...	...	.20	12
2. F. K.	1944	4 plus	....	6.8	3.9	2.9	20	..	2.1	18.8	57.1	...	...	1.0	....
	1946	4 plus	6.3	5.7	3.6	2.1	..	10	3.3	....	....	...	...	....	6
	1947	4 plus	7.0	...	...	...	..	..	2.5	19.1	58.7	...	...	....	....
3. C. S.	1939	....	....	5.3	3.7	1.6	5	..	13.9	....	....	162	130	.30	8.6
	1945	neg.	....	5.9	4.7	1.2	..	22	5.4	18	52	145	...	.40	11
	1947	4 plus	12	3.8	...	...	..	..	2.7	41.7	75.9	116	...	9.0	....
4. R. W.	1932	....	....	...	...	...	5	..	....	....	....	...	...	....	8
	1942	....	....	6.7	4.7	2.0	..	..	....	....	....	...	...	....	....
5. R. B.	1934	....	....	...	...	...	..	..	....	....	....	...	...	.15	4
6. L. C.	1945	4 plus	5	6.6	4.1	2.5	50	..	8.0	15	31	231	130	.25	12
	1947	4 plus	15	5.4	3.5	1.9	60	..	5.0	19.6	40	184	...	....	....
	1948	4 plus	12	...	...	...	..	..	4.0	....	....	140	...	2.8	....
7. W. C.	1945	neg.	....	6.6	4.5	2.1	20	..	3.9	17	33	131	96	.15	6
	1948	....	3	...	...	...	..	..	....	....	....	...	...	tr	....
	1951	4 plus	11.5	4.9	2.5	2.4	..	90	7.6	22	57.2	164	...	.7	....
Patients without Clinical Signs of Hepatic Dysfunction															
8. D. W.	....	....	....	....	...	...	..	..	....	....	....	...	...	....	....
9. R. S.	1936	....	....	...	...	...	..	..	....	....	....	136	...	....	7
	1937	....	....	4.6	...	...	5	..	....	....	....	160	...	....	7
10. E. H.	1934	....	....	6.0	4.8	1.2	5	..	....	....	....	144	124	.20	6
	1943	3 plus	....	5.8	4.3	1.5	..	..	....	....	....	138	...	.50	....
11. J. G.	....	....	....	...	...	...	..	..	....	....	....	...	...	....	....

diffusely nodular cirrhotic liver, a moderately enlarged spleen and extensive bilateral bronchopneumonia. The findings in the brain were those seen in Wilson's disease.

CASE 3. C. S., a fifteen year old boy, was first admitted to the Montefiore Hospital in 1939 because of generalized rigidity, loss of motor power and tremors of the left arm and leg. At the age of nine years the patient had ascites, edema of the ankles and hepatosplenomegaly. He had several paracenteses at another hospital. One month before admission involuntary movements of the left arm and leg were noted. This was followed in forty-eight hours by champing movements of the jaw, dysarthria and extreme weakness. For three weeks prior to admission he lay in bed assuming a variety of rigid postures, moaning constantly and exhibiting frequent fine tremors of the hands and feet.

Physical examination revealed a pale, semicomatose, dehydrated, febrile, acutely ill boy of fifteen. There were bilateral Kayser-Fleischer rings. The spleen was 3 cm. below the costal margin. Neurologic examination revealed that the patient was aware of his environment but anarthric. The head was hyperextended and there was marked rigidity of the trunk and extremities. Sucking movements of the lips and champing movements of the jaw were present. There were frequent changes in tonus associated with twitching and convulsive movements. The deep tendon reflexes were hypoactive. The big toes were maintained in dorsiflexion.

During the first three months the patient remained acutely ill and stuporous. There were repeated convulsive seizures and his temperature rose at irregular intervals to 107°F. Subsequently the clinical picture gradually improved. The patient's speech returned but remained dysarthric. Spasticity and rigidity also diminished to the extent that he became ambulatory. After his discharge from the hospital in 1941 he was observed in the clinic. He was readmitted in 1944 for progression of tremor and rigidity. The liver was still not palpable but splenomegaly was present. The patient had a clumsy, stiff-legged, broad-based gait. There was spasticity, hypertonicity and weakness of all extremities. "Wing beating" of the arms was noted. Babinski signs were present bilaterally. In the next three years the patient's illness progressed slowly but steadily. There was concomitant impairment in hepatic function as indicated by liver function tests. (Table I.) In September, 1947, he began to vomit. Subsequently, he became febrile, jaundiced and comatose. Ascites and edema were noted. Two months later he died with a B. aerogenes septicemia and bronchopneumonia. This was fourteen years after the onset of his illness. Post mortem examination was not permitted.

CASE 4. R. W., a fifteen year old white female, was first admitted to the Montefiore Hospital in 1932 because of tremors of her hands and difficulty in talking of several months' duration. She is the sister of D. W. (Case 8). Her parents were first cousins. One brother died of encephalitis in his mid-twenties. Two other sisters had Kayser-Fleischer rings. At the age of seven years the patient had a transient episode of jaundice and a "swollen liver." She was confined to bed for one year. At the age of eight she had influenza and, at twelve, a diagnosis of rheumatic fever was made. At the age of fourteen she became drowsy and developed a tremor. At fifteen she developed dysarthria and dysphagia.

Physical examination revealed bilateral Kayser-Fleischer rings. There was no hepatosplenomegaly. Neurologic examination showed euphoria, dysarthria, hypertonicity, a bilateral tremor increased by activity and "wing beating." She walked with a broad-based gait, her arms swinging in wide arcs.

The course, which was progressively downhill, was marked by episodes of fever and drowsiness. In 1943 she vomited 300 cc. of blood. The following day she became jaundiced, febrile and comatose. She had several other bouts of hematemesis and then died. This was nineteen years after the onset of her illness. Throughout her course the few hepatic function tests that were done were normal. (Table I.) Postmortem examination was limited to the brain and revealed changes characteristic of hepatolenticular degeneration.

CASE 5. R. B., a twenty-five year old female, was admitted to the Montefiore Hospital in 1934 because of tremors of the upper extremities of nine months' duration. Since she was eleven years old she had had frequent nosebleeds. Menses started at the age of eleven and occurred every three months. When she was sixteen, there was profuse menorrhagia. At twenty-four she had headaches, spots before the eyes, nausea and vomiting. She had splenomegaly and was admitted to another hospital where she was thought to have a blood dyscrasia. The hemo-

globin was 35 per cent, the red blood cell count 3.55 million and the white blood cell count 3,400. The bleeding time, clotting time and fragility tests were normal. In 1934 a diagnosis of Banti's syndrome was made. During laparotomy a 975 gm-spleen was removed and the liver was found to be markedly contracted and had a hob-nailed appearance. Six months ltaer she was readmitted to another hospital because of bleeding gums, petechiae, ecchymoses, tremors of the upper extremities, moderate rigidity and emotional instability. Bilateral Kayser-Fleischer rings were noted for the first time. The hemoglobin was 58 per cent, the red blood cell count 3.83 million, the platelet count 230,000 and the white blood cell count 14,200. Bleeding and clotting times were normal. She was admitted to the Montefiore Hospital in July, 1934, and was observed for three and one-half months, during which time she was emotionally unstable. Physically, there was no overt progression of the disease. There was a moderate anemia and the platelet count was 100,000. Bleeding time, clotting time and clot retraction, however, were all normal.

The patient was subsequently transferred to another institution for long-term care. Her course there remained fairly stationary until August, 1935, when she committed suicide, about sixteen years after the onset of her illness.

Findings at postmortem examination and the clinical course of this patient have been described in detail by Rabiner et al.[13] Suffice it to say here that there was cirrhosis of the liver and examination of the brain showed abnormalities throughout, most marked in the basal ganglia, ventral and lateral thalamic nuclei and hypothalamus.

Case 6. L. C., a thirty year old white male, brother of W. C. (Case 7), was first admitted to the Montefiore Hospital in 1945 because of tremor of the right arm of one years' duration. The patient had been a labile diabetic since the age of twenty, requiring 20 to 80 units of protamine zinc insulin daily, and had been consuming at least 1 quart of whiskey a week for many years. About one year prior to admission the patient noted a tremor of his right arm which was aggravated by activity.

Physical examination revealed some spider angiomas over the upper part of his body and Kayser-Fleischer rings bilaterally. The liver was palpable 2 cm. below the costal margin; the spleen was barely palpable. Neurologic examination revealed a slow scanning speech and mask-like facial expression with a vacuous smile. There was a coarse tremor of the right arm and "wing beating." His gait was ataxic.

During his stay in the hospital the tremor became worse. In 1945 he required a left nephrectomy for nephrolithiasis and pyonephrosis. In 1947 his liver was palpable 5 cm. below the costal margin. Tests for hepatic function showed impairment throughout his course in the hospital. (Table 1.) In May 1948, four years after the onset of his illness, the patient developed pharyngitis which was followed by progressive drowsiness, icterus, several bouts of hematemesis and death.

Postmortem examination showed the following significant findings: The liver weighed 1,450 gm. and was grossly nodular. Its architecture was completely distorted in a manner compatible with a diagnosis of multilobular cirrhosis. The spleen weighed 550 gm. There were numerous esophageal varices. Findings in the brain were consistent with those seen in hepatolenticular degeneration.

Case 7. W. C., a twenty-two year old white male, was first seen at the Montefiore Hospital in 1945 because of tremors, difficulty in walking and dysarthria. The patient had consumed large quantities of alcohol since the age of twelve. One of his brothers is reported as Case 6. Another brother is a chronic alcoholic. Four other siblings are normal. At the age of sixteen years the patient noted a tremor of his right hand and, shortly afterward, of his left hand. The tremor was aggravated by activity. At eighteen he developed dysarthria and an unsteady gait.

Physical examination on his first admission showed bilateral Kayser-Fleischer rings. Liver and spleen were not palpable. Neurologic examination showed euphoria and dysarthric speech. There was a bilateral intention tremor. "Wing beating" of both arms was noted. His gait was broad-based and stiff-legged. The deep tendon reflexes were slightly hyperactive.

The patient remained in the hospital until 1949. He was readmitted in 1951 because of weight gain, right upper quadrant discomfort, abdominal distention and swelling of the ankles. Physical examination showed numerous spider angiomas distributed over the upper half of his body. The abdomen was moderately distended with fluid. The spleen was felt 4 cm. below the costal margin. The liver edge was not palpable

but there was some tenderness on palpation of the right upper quadrant. Mild pitting edema of the legs had developed. There was little progression in the neurologic process. The results of liver function tests revealed progression of hepatic damage. (Table 1.) Fluoroscopy after barium swallow demonstrated esophageal varices. This patient is still under observation, fourteen years after the onset of his illness. He receives a high carbohydrate, high protein, low fat and low salt diet. When necessary, injection of a mercurial diuretic has successfully controlled the ascites and the edema of the legs.*

CASE 8. D. W., a fifteen year old female, was admitted to the Montefiore Hospital in 1931 because of tremor of the hands and difficulty in walking of two years' duration. She was the sister of R. W. (Case 4). At the age of thirteen years the patient developed a tremor of the right hand. At this time there were several episodes of diplopia and the slightest emotional stimulus provoked excessive laughter. A year later tremor of the left hand began.

On physical examination a Kayser-Fleischer ring was not identified although there was pigmentation of the limbal margin. There was no hepatosplenomegaly. Neurologic examination showed an emotionally unstable female. There was an intention tremor bilaterally, slow thick speech, moderate rigidity, hypertonicity and mild hyperreflexia.

Shortly after admission marked personality changes were noted and she was transferred to a psychiatric institution where she died with Vincent's angina in 1932, four years after the onset of her illness. At no time was there any clinical evidence of liver disease. Liver function studies were not carried out in the month that the patient was in Montefiore Hospital. Postmortem examination was not obtained.

CASE 9. R. S., a twenty-three year old white female, was admitted to the Montefiore Hospital in 1936 because of tremors of seven years' duration. At the age of sixteen years she noted a tremor of her left hand which involved all the extremities within one year. Subsequently, there was dysarthric speech, a change in facies, episodes of involuntary laughter and diplopia. At eighteen years she had repeated attacks of unilateral flexion spasm of the trunk and extremities followed by stupor. From the age of twenty there was steady progression. On admission she could no longer walk or feed herself.

Physical examination showed bilateral Kayser-Fleischer rings. Neurologic examination revealed a constantly smiling facies, spasmodic tremor of the head and "wing beating" of the upper extremities. There was rigidity, poor coordination and dysarthric speech. Abdominal skin reflexes were absent and the big toes were constantly dorsiflexed. The neurologic signs advanced slowly in the next three years, the patient spending almost all her time in bed. In 1939 personality changes became severe and it became necessary to transfer the patient to a psychiatric institution where convulsive movements of the trunk and extremities were noted. She became febrile and comatose and died one week after being admitted to the psychiatric institution. The duration of the illness in this case was ten years. The results of the few liver function tests performed were within the limits of normal. (Table 1.)

Necropsy at another hospital showed the following significant findings: The liver weighed 1,225 gm. and was firm and nodular. Its appearance was characteristic of multilobular cirrhosis. The spleen was not remarkable. Findings in the brain were consistent with a diagnosis of hepatolenticular degeneration. This case has been reported by Jervis and Moore.[11]

CASE 10. E. H., a sixteen year old white female, twin sister of B. H. (Case 1), was first admitted to the Montefiore Hospital in 1934 because of tremor of the hands of one year's duration.

Physical examination showed bilateral Kayser-Fleischer rings. Hepatosplenomegaly was not present. Neurologic examination showed dysarthria, tremor of the left hand, ataxia of all extremities, decreased associated movements in the left upper extremity, weakness and fatiguability of the muscles of both hands and cogwheel hypertonicity.

During her first admission she developed tremors of the lower extremities and "wing beating." Following discharge from the hospital in 1935 she became progressively unsteady on her feet and the manual tremor increased. She was readmitted in 1940. In addition to marked progression of the other neurologic signs there was euphoria and paranoid ideation. During

* Since we completed this paper, this patient was transferred to the Rockefeller Institute Hospital where studies of copper and amino acid metabolism were done. He died four months after his transfer. Postmortem examination revealed cirrhosis of the liver, splenomegaly and esophageal varices. Examination of the brain had not been completed at the time of this writing.

this admission she became incontinent of urine. She was discharged in 1941. During her third admission from 1941 to 1943 she was bedridden. During her fourth and final admission in 1943 the course was steadily downhill. At no time was there any clinical or laboratory evidence of liver damage except for a three plus cephalin flocculation test during a terminal bout of bronchopneumonia, eleven years after the onset of her illness. (Table 1.) Postmortem examination was not obtained.

Case 11. J. G., a twenty-four year old white male, was first admitted to the Montefiore Hospital in 1934 because of weakness and tremors of the extremities of six years' duration. At the age of sixteen years the patient became a behavior problem. At eighteen years skillful movements were performed with difficulty and choreiform movements appeared. His hands became spastic, his legs unsteady, and he developed a tremor of his head.

Physical examination showed bilateral Kayser-Fleischer rings. Neurologic examination showed a wobbling gait, incoordination, dysarthria, tremors and "wing beating."

He was discharged from the hospital in 1935 and observed by his physician for five years. His course was slowly progressive. When he was readmitted in 1940, severe progression of his neurologic symptoms had occurred. He was anarthric and bedridden. There was generalized rigidity, a coarse rhythmic tremor of the head, trunk and extremities. There was left ankle clonus, absent superficial abdominal and cremasteric reflexes and a probable right supranuclear seventh nerve paresis. Shortly after admission the patient developed bronchopneumonia and died, fourteen years after the onset of his disease. At no time was there any clinical evidence of liver damage. Liver function tests were not performed.

Significant findings at postmortem examination were as follows: The liver weighed 1,500 gm. and was firm and nodular. The findings were typical of diffuse nodular cirrhosis of the liver. The spleen weighed 250 gm. A lung abscess was present in the left upper lobe. In addition to the changes usually seen in hepatolenticular degeneration there was severe involvement of the motor and premotor areas of the cerebral cortex.

COMMENTS

Onset of Illness. The first symptom in five of the eleven cases described was of hepatic origin. In Case 1 a diagnosis of cirrhosis of the liver was made at laparotomy to disclose the cause of ascites and vomiting at the age of ten, two years before the onset of dysarthria. In Case 2 splenomegaly was found during an otherwise normal pregnancy four years prior to the onset of neurologic symptoms. Another patient (Case 3) was admitted to the hospital because of ascites, edema of the ankles and hepatosplenomegaly at the age of nine, six years before the onset of tremor. There was hepatomegaly and transient jaundice eight years prior to the onset of neurologic complaints in Case 4, and in Case 5 splenomegaly, cirrhosis and a bleeding tendency began fifteen years prior to neurologic symptoms.

There are several reports in the literature of cases in which hepatic damage preceded neurologic symptoms. For instance, in two of Wilson's original six cases[1] jaundice quite clearly preceded neurologic symptoms. Barnes and Hurst[8] found symptoms of liver disease initially in each of their four cases. They called attention to the fact that one of their patients died with cirrhosis before developing neurologic symptoms. Of the six cases reported by Herz and Drew[7] frank hepatic damage preceded neurologic symptoms in two.

The initial symptom in our other six cases was neurogenic, i.e., tremor, dysarthria, difficulty in walking, incoordination. It is interesting to note that there are reports in the literature in which the onset was neurogenic in every case. This was true of the nine cases reported by Sweet, Gray and Allen,[6] the four cases reported by Homburger and Kozol[5] and the recent series of five cases reported by Denny-Brown and Porter.[12]

Kayser-Fleischer rings may have been present for several years prior to their discovery but no search was made for them until the appearance of neurologic symptoms suggested the possibility of hepatolenticular degeneration. In our series the diagnosis of Wilson's disease was never made prior to the appearance of a neurogenic disorder.

Frequency of Clinically Demonstrable Hepatic Dysfunction. In seven of our eleven patients symptoms and signs of hepatic disease were prominent during the course of illness. As mentioned previously, five of these manifested symptoms of liver disease from the onset. Subsequently, other signs developed. Thus Case 1 required numerous paracenteses after an exploratory laparotomy, at which time a diagnosis of cirrhosis was made. Splenomegaly developed six years after the onset

and, prior to death, the patient had a bout of hematemesis. In Case 2 ascites and jaundice appeared two years after the discovery of hepatosplenomegaly. A diagnosis of lobular cirrhosis of the liver was made during a tubal ligation one year prior to the onset of tremor.

Laboratory tests of hepatic function showed abnormal values in five of the seven cases with clinical evidences of liver dysfunction. In the sixth case a bromsulfalein excretion test and icterus index early in the course and serum protein determinations carried out later were

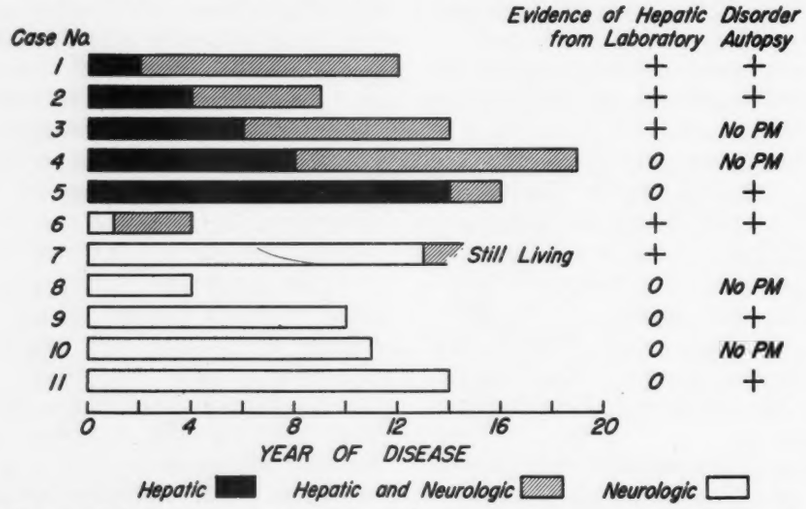


FIG. 1. Relative onset of hepatic and/or neurologic signs and symptoms in Wilson's disease.

Case 3 had jaundice and ascites terminally. Jaundice and hematemeses occurred shortly before death in Case 4. Splenomegaly and symptoms of hypersplenism were present in Case 5.

Two of the patients who had no symptoms of liver disease at the onset subsequently developed signs of hepatic insufficiency. One year after the onset of his illness Case 6 developed hepatosplenomegaly and spider angiomas. Terminally he became jaundiced and had several episodes of hematemesis. In Case 7 ascites, edema, splenomegaly, spider angiomas and esophageal varices proven by roentgenogram appeared fourteen years after the onset of his illness. Both of these patients were severe alcoholics since their early teens. The role of alcohol or dietary deficiencies in the development of cirrhosis in these cases cannot be determined.

The frequency of the clinical signs and symptoms of hepatic damage is listed in Table II. Figure 1 summarizes the course of the disease in the patients.

Hepatic Function Tests. Table I shows the pertinent findings in the commonly performed liver function tests. It is not feasible to enumerate all the tests for hepatic function that were carried out in these patients; hence only significant and representative ones have been listed.

normal. Serum bilirubin and icteric index were normal in the seventh case.

In the patients with clinical evidence of liver disease the cephalin flocculation test was 4 plus in the four instances in which it was used. There was impairment in the excretion of bromsulfa-

TABLE II

FREQUENCY OF SIGNS AND SYMPTOMS OF LIVER DISEASE IN ELEVEN CASES OF WILSON'S DISEASE

	No. of Cases
Splenomegaly	6
Ascites	4
Jaundice	4
Hepatomegaly	4
Hematemesis	3
Gastro-intestinal disturbances	3
Spider angiomas	2
*Varices	1
Bleeding from other sources	2

* Looked for during life in three patients, two of whom had clinical liver disease.

lein in five of six cases; it was normal in Case 4 in which liver disease played a prominent role. The thymol turbidity test was abnormal in the four cases in which it was performed. There was a significant fall in the total serum protein in five of six cases. In three of four cases with clinical signs of hepatic impairment the alkaline phosphatase was greater than five Bodansky units on at least one occasion. The prothrombin

time was prolonged in two of the four cases in which it was done. In another, there was prolongation in the diluted specimen. In one patient (Case 11) in whom severe bleeding was the most outstanding feature no prothrombin time was done. Total serum cholesterol was low in each of four cases. The esterified fraction, however, was normal. Serum bilirubin was within normal limits except in two patients who were jaundiced terminally. In several instances the tests became more abnormal as the disease became progressively more severe.

Little can be said about liver function tests in the four cases showing no clinical signs of hepatic damage since few liver function tests were performed.

Sweet, Gray and Allen[6] studied liver function tests in nine cases of Wilson's disease without clinical evidence of hepatic failure. Each of their patients had at least one abnormal liver function test. They found the colloidal gold, bilirubin excretion test and the prothrombin time more sensitive indicators of hepatic change than the alkaline phosphatase, serum globulin, cholesterol fractionation and bromsulfalein excretion. They did not use the cephalin flocculation or thymol turbidity tests. Herz and Drew[7] in a study of six patients with Wilson's disease found abnormal values in the hepatic function tests in four of their cases. A positive cephalin flocculation test was obtained more frequently than a fall in serum albumin or retention of bromsulfalein. Homburger and Kozol,[5] in a study of four cases, considered the cephalin flucculation test the only one that reflected the patient's clinical condition. Unlike other observers, we frequently found abnormal values in alkaline phosphatase, total serum protein and total serum cholesterol. This may be due to the fact that in our series systematic study of liver function was undertaken only in cases with clinical signs of liver disease while other observers also included cases without obvious hepatic failure.

Cause of Death. Of the eleven patients in this series, only one is alive and under observation. The duration of life in the other ten varied from four to nineteen years, with nine patients living nine or more years. Unlike some observers,[7] we were unable to correlate the severity of liver disease with the course or duration of illness.

Of the seven patients with clinical evidence of liver disease only one (Case 7) is alive. Four died with signs of advanced hepatic failure. Case 1 gradually went into coma and died following a massive hematemesis. Another patient (Case 3) succumbed to a B. aerogenes septicemia when he was comatose, jaundiced and had ascites and edema. Cases 4 and 6 became jaundiced, comatose and had several large hematemeses. Cases 2 and 5 are the only ones in whom hepatic failure did not directly cause death. As previously mentioned, Case 2 died during bronchopneumonia and Case 5 committed suicide.

In the four cases without clinical evidence of liver damage during life, hepatic failure was not responsible for death. Case 8 died from Vincent's angina, Case 9 gradually went into coma prior to death and two patients (Cases 10 and 11) died with bronchopneumonia.

Postmortem Observations. Complete postmortem examinations were made in six of our patients; in a seventh only the brain was examined. In all there was advanced multilobular cirrhosis of the liver. The liver was generally small, firm and nodular. The nodules varied in size from several mm. to 3 or more cm. and were separated by bands of fibrous tissue. Splenomegaly was present in five of six cases but there was no other change on gross or microscopic examination. Esophageal varices were found in two of the six cases. Both of these patients had hematemeses prior to death. Lesions characteristic of Wilson's disease were found in every brain.

SUMMARY AND CONCLUSIONS

Eleven cases of Wilson's disease were reviewed in order to determine the incidence of clinical evidence of hepatic dysfunction. Clinical signs of liver disease were apparent in seven patients. Five of these developed symptoms of liver disease prior to any neurogenic disorder; in the other two, symptoms and signs of hepatic failure appeared during the course of the illness.

Laboratory findings confirmed the clinical impression of hepatic insufficiency. They added little in the way of diagnosis.

In the six livers examined at postmortem the findings were typical of advanced multilobular cirrhosis.

Based on our study, it would appear that liver dysfunction is not unusual in Wilson's disease. This fact has not been sufficiently emphasized in the literature where it is still frequently stated that hepatic disease cannot be diagnosed clinically. On the basis of our experience frank hepatic decompensation is common in hepatolenticular degeneration.

Acknowledgment: We wish to thank Dr. Theodore J. C. von Storch and Dr. Martin G. Netsky for their aid and advice in the preparation of this paper. We are grateful to Mrs. Bertha W. Wechsler for her technical assistance. Dr. Nathan Savitsky allowed us to report Case 9. Dr. H. A. LaBurt and Dr. A. M. Rabiner supplied us with additional information about cases 6, 10 and 11.

REFERENCES

1. Wilson, S. A. K. Progressive lenticular degeneration. *Brain*, 34: 295, 1912.
2. Wilson, S. A. K. Neurology, pp. 806–831. Baltimore, 1940. The Williams & Wilkins Co.
3. Carter, H. R. Hepato-lenticular degeneration; a report of four cases in a Spanish American family with differential diagnosis and treatment. *J. Nerv. & Ment. Dis.*, 107: 150, 1948.
4. Freedberg, H. Hepato-lenticular degeneration. Report of one case with severe portal cirrhosis and splenomegaly. *Ann. Int. Med.*, 22: 418, 1945.
5. Homburger, F. and Kozol, H. L. Hepato-lenticular degeneration. *J. A. M. A.*, 130: 6, 1946.
6. Sweet, W. H., Gray, S. J. and Allen, J. G. Clinical detection of hepatic disease in hepato-lenticular degeneration. Report of nine cases. *J. A. M. A.*, 117: 1613, 1941.
7. Herz, E. and Drew, A. J., Jr. Hepato-lenticular degeneration; analysis of dyskinetic phenomena; relation of degree of hepatic damage to course of disease; nervous disorders in ordinary disease of the liver. *Arch. Neurol. & Psychiat.*, 63: 843, 1950.
8. Barnes, S. and Hurst, E. W. Hepato-lenticular degeneration. *Brain*, 48: 279, 1925.
9. Gutman, A. B. and Hanger, F. M., Jr. Differential diagnosis of jaundice by combined serum phosphatase determination and cephalin flocculation test. *M. Clin. North America*, 25: 837, 1941.
10. Gray, S. J. The colloidal gold reaction of blood serum in diseases of the liver. *Arch. Int. Med.*, 65: 524, 1940.
11. Jervis, G. A. and Moore, J. Progressive lenticular degeneration. *Psychiatric Quart.*, 16: 357, 1942.
12. Denny-Brown, S. and Porter, H. The effect of B.A.L. on hepato-lenticular degeneration. *New England J. Med.*, 245: 917, 1951.
13. Rabiner, A. M., Joachim, H. and Freiman, I. S. Hepato-lenticular degeneration following splenectomy; interrelationship of the reticuloendothelial and central nervous systems. *Ann. Int. Med.*, 14: 1781, 1941.

Hypokalemia in Liver Cell Failure*

EDWARD L. ARTMAN,† M.D. AND ROBERT A. WISE,‡ M.D.

Long Beach, California *Houston, Texas*

IN July, 1950, hypokalemia was noted in a seriously ill comatose patient with portal cirrhosis (Case O. H., Fig. 1). In addition to conventional therapy we gave potassium parenterally and orally. The favorable response obtained in this case prompted a review of the literature and extension of our observations to similar cases.

Several authors during the past ten years have made observations on the serum potassium and other electrolytes in cirrhosis during phases of hepatocellular failure.[1–4,8] Latner[3] observed hypokalemia in two of five patients with hepatic coma. He attributed the low serum potassium values to the use of intravenous glucose (glucose loading) and advocated the addition of potassium chloride to the intravenous solutions used. Amatuzio and collaborators reported that in their studies of patients with severely decompensated portal cirrhosis, hypokalemia was common and that sodium, calcium and phosphorus levels were also frequently low.[8] Other authors, however, at the time our study was completed had not emphasized the significance of replacing potassium in the acutely decompensated cirrhotic. In recent reviews of causes of hypopotassemia, hepatocellular damage was not mentioned.[5–7]

We have studied thirty patients with cirrhosis in hepatocellular failure and found hypopotassemia in twenty-five.

METHOD

The records of thirty patients with cirrhosis were selected. In these cases the diagnosis was well established, there was ample evidence of acute liver cell failure and studies of potassium and other serum electrolytes had been obtained.

The clinical diagnosis was confirmed by needle biopsy (posterolateral approach) in nine instances, necropsy in eight, surgery in one. Base line studies of liver function were made using serum bilirubin, cephalin flocculation test, thymol turbidity test, total protein, prothrombin time, alkaline phosphatase and urine urobilinogen. Determinations of sodium, potassium, total base, chlorides, blood urea nitrogen were obtained, as well as electrocardiograms. The biochemical analyses were repeated as clinical management of the patient dictated.

The Coleman flame photometer was used for serum sodium and potassium determinations. The lower limit of normal for serum potassium in this laboratory is 3.8 mEq./L. Serum sodium estimations were always carried out but are not reported here.

Treatment in most cases consisted of bed rest, intravenous glucose, methionine and choline, water soluble multivitamins including niacin, vitamin K, thiamin and ascorbic acid. Water and electrolyte balance was maintained. Adrenal cortex (lipo-adrenal) was used in many cases. Transfusions were given as indicated. Efforts to control ascites were made by use of mercuhydrin and cation absorbing resins. Several cases required paracentesis.

It should be pointed out that this series is primarily one made in retrospect and that often the potassium studies were not repeated frequently enough to warrant detailed conclusions. However, six cases are presented in which the problem was studied in more detail.

CASE REPORTS

Analysis of these thirty cases reveals that twenty-five had serum potassium levels below 3.8 mEq. on at least one determination; seventeen cases were observed to have hypokalemia only for a short time after admission; eight showed persistently low potassium in spite of adequate diet and partial replacement therapy for long periods of time. Four of our cases showed

* From the Departments of Medicine, Veterans Administration Hospital and Baylor University College of Medicine, Houston, Tex.

† Present address: Veterans Administration Hospital, Long Beach, Calif.

‡ Present address: Humble Oil & Refining Co., Box 2180, Houston 1, Tex.

normal levels and one had a slightly increased level, 4.9 to 6.5 mEq. (terminal value with intestinal bleeding).

Most of these patients were alcoholics with cirrhosis and during hospital admission for study were either in an acute hepatocellular phase of early cirrhosis or showed acute hepatocellular damage in the course of chronic cirrhosis. Six of the cases that were studied more thoroughly are reported below:

Case I. O. H., a fifty-four year old white chronic alcoholic man, was admitted on July 25, 1950. Admission complaints included nausea and vomiting but a good history could not be obtained because of incoherence. History from his wife indicated that he had consumed 1 pint or more of whiskey daily for several years and that she had observed jaundice in February, 1950. Thereafter he had required paracentesis.

Examination revealed an acutely ill, delirious, slightly obese man with ascites, jaundice and clubbing of the fingers. Admission laboratory work included: white blood cells, 12,600; red blood cells, 4.2 million; hemoglobin 13.0 gm.; blood urea nitrogen, 7.3 mg. per cent; total protein 6.6 gm. per cent with albumin 2.9 and globulin 3.7; serum bilirubin 1.8 mg. per cent; thymol turbidity 9.0 McLagan units; prothrombin time 26 seconds; calcium 8.4 mg. per cent.

On the fourth hospital day, in spite of supportive therapy, he had gradually become comatose and examination revealed a resistive stiffness of his extremities and neck. The spinal fluid at the time was normal. Skin and tongue showed marked dehydration. Diarrhea was observed to be present. On this date the serum potassium was 1.9 mEq./L., the serum sodium was 126 mEq./L. and the serum chlorides 82 mEq./L. The Q-T interval in the electrocardiogram was prolonged. The patient was treated with intravenous potassium chloride, 5 per cent sodium chloride in amounts calculated for replacement, and calcium gluconate, penicillin and streptomycin. An extremely critical state prevailed for two days with need for aspiration of the trachea, parenteral feeding and replacement of fluids and vitamins. By July 26, 1950, he began to take fluids orally and slowly improved from this point on. On August 7, 1950, the BSP test showed 20 per cent retention in thirty minutes. By December, 1950, BSP retention was 20 per cent in thirty minutes, the cephalin flocculation test was negative, serum bilirubin 0.4 mg. per cent and prothrombin time 80 per cent.

Figure 1 indicates serum potassium levels and potassium replacement in mEq. per twenty-four hours throughout the period of observation.

Case II. W. G., a thirty-nine year old white male cook, was admitted on December 6, 1950, in coma. He had been a chronic alcoholic for many years until three months earlier, when nausea, vomiting, diarrhea and abdominal swelling developed. In the month immediately prior to admission he quit work because of diarrhea. Immediately prior to admission streaks of bright red blood were noticed in the vomitus and stools.

Examination on admission revealed intense icterus of the sclerae and skin in a semicomatose patient with a temperature of 102°F. rectally. Hepatomegaly, ascites, slightly prominent abdominal veins and pitting edema over the legs were present. The tendon jerks were hypoactive. Spider nevi were noted over the face and shoulders. There was a reduction of axillary and an absence of chest hair. The laboratory findings on admission revealed a marked anemia, normal white count, positive bile and albumin in the urine. The serum bilirubin was 9.1 mg. per cent; prothrombin activity 35 per cent; thymol turbidity 14 McLagan units; total protein 7.2 gm. per cent with albumin 2.8 gm. and globulin 4.4 gm.; total base 147 mEq./L.; blood urea nitrogen 31 mg. per cent; calcium 10.5 mg. per cent; inorganic phosphorus 2.7 mg. per cent. Serum amylase was 69 mg. per cent and on repeated determinations showed a rise to 130 mg. per cent.

The patient was considered critically ill and to have acute liver failure and acute pancreatitis. He was given general supportive treatment as outlined in the discussion of methods. Within a week he was rational and free of peripheral edema. The temperature remained elevated and liver function tests were abnormal for several weeks. By March 10th the red blood count and hemoglobin had returned to a borderline normal. The serum bilirubin, thymol turbidity test and prothrombin activity were normal, and the urine was negative for urobilinogen. The total serum was protein 6.2 gm. per cent. A punch biopsy of the liver showed portal cirrhosis.

On March 16, 1951, the temperature, which had previously been normal, rose to 100°F. and the patient began to notice general malaise. The temperature remained elevated. On March 19,

1951, icterus of the sclerae was noted and the patient became hallucinatory. During the ensuing few hours he rapidly lapsed into coma and remained in a deep coma until March 30th, a period of eleven days. The clinical impression of homologous serum hepatitis was entertained because of the use of whole blood and plasma during the previous coma. Supportive measures used in the first coma, as well as supplementary potassium, were started immediately. In addition, human serum albumin, 100 gm., was given during the second twenty-four-hour period of coma. On the second day the patient was intubated with a polyethylene intratracheal airway. Gastric feeding by an intragastric tube was instituted using a formula of carbohydrate, 300 gm., protein, 100 gm., in a 2,400 cc. volume. This mixture supplied approximately 53 mEq. potassium per day. During the comatose period adequate hydration and urinary output were maintained. An average total intake of between 4,000 and 5,000 cc. per twenty-four hours was required because of profuse sweating. The potassium replacement values shown in Figure 2 demonstrate both oral and intravenous potassium replacement. On March 30, 1951, the patient regained consciousness and within a few hours became completely rational. On the following day he was able to take a full diet. During the period of recovery serum potassium levels were lower than during coma. Potassium replacement at that time was by means of diet alone which supplied approximately 100 mg. of potassium daily. By April 9, 1951, a normal serum potassium level was observed. Since that time occasional serum potassium determinations have ranged within the lower limits of normal. All liver function tests returned to normal or

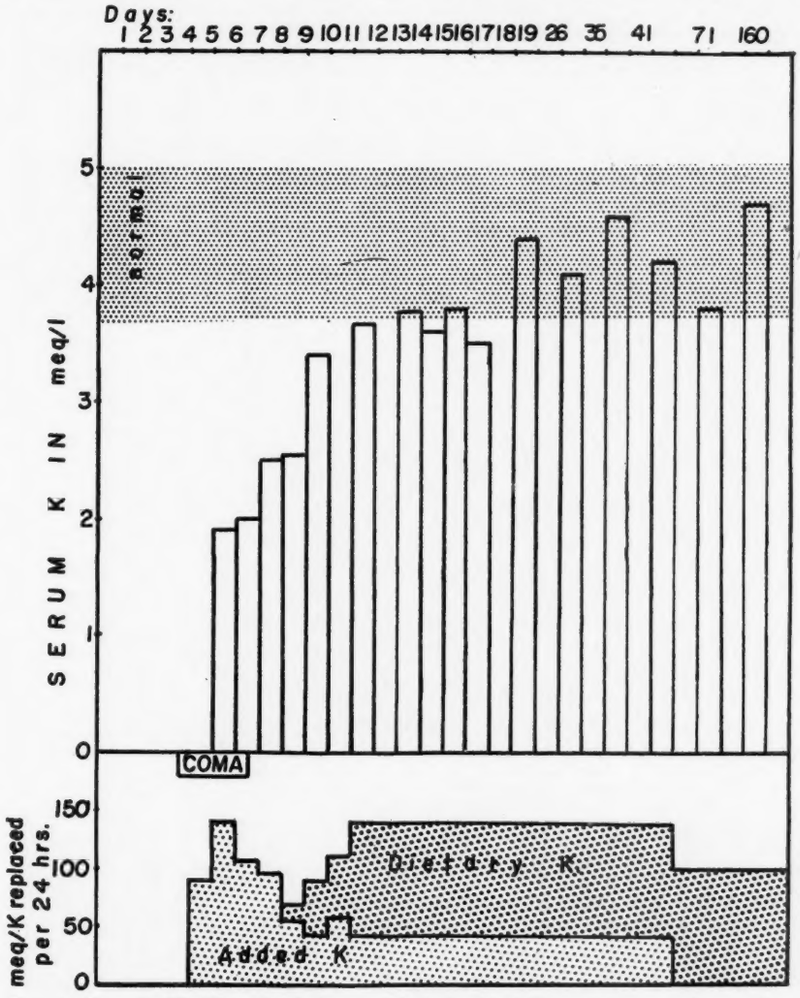


FIG. 1. Case O. H. The stippled area labeled added K represents oral as well as intravenous potassium salts.

stabilized by October, 1951, and have remained so until December 28, 1951.

During the period of coma the prothrombin activity, which had previously reached normal values, dropped abruptly to 15 per cent and did not return to normal for seven months. During both periods of coma there was a sharp fall in the serum phosphorus with return to normal during the recovery period. The total base and total serum protein estimations were within normal limits during the coma period. The electrocardiogram, which had been normal until the onset of coma, showed a prolongation of the P-R interval and quite marked flattening and broadening of the T waves. These changes persisted until the serum potassium had returned to normal. (Fig. 2.)

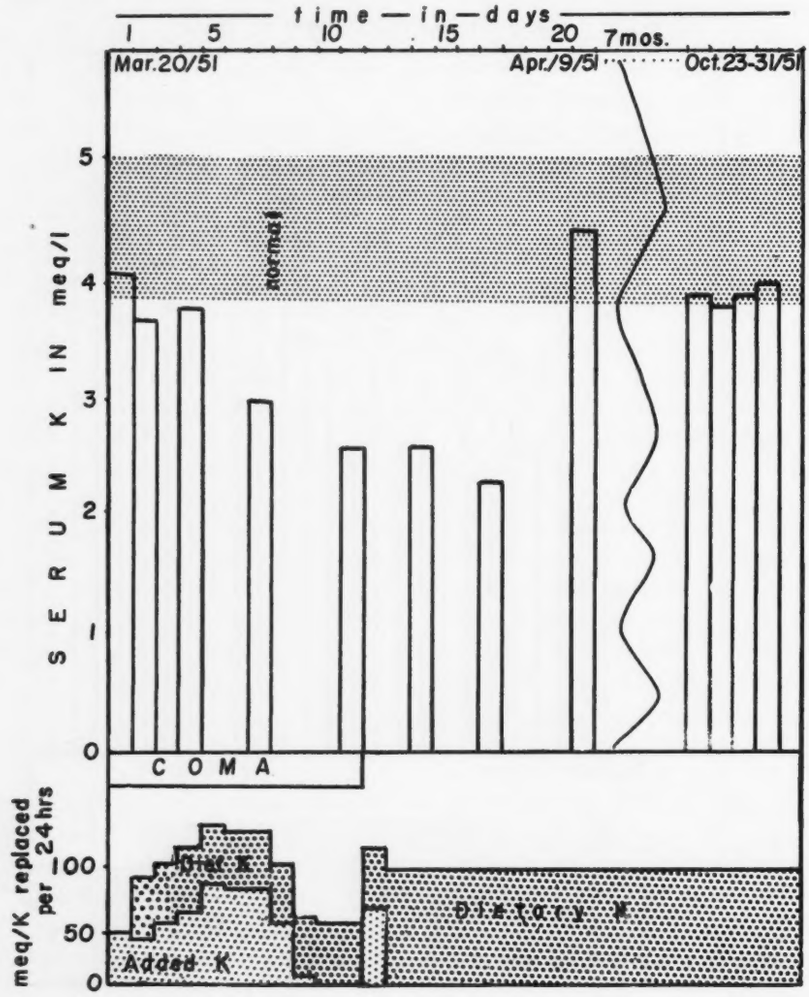


FIG. 2. Case W. G. Data covering second coma and follow-up period. The stippled area labeled added K represents oral as well as intravenous potassium salts.

CASE III. O. B., a thirty-one year old man with ten years of chronic alcoholism, was admitted on June 6, 1951, following the onset of jaundice and stuporous condition several days previously. On admission the patient was severely ill, hallucinatory, stuporous and icteric. Temperature was 103°F. rectally. Hepatomegaly and massive ascites were present. The pubic and axillary hair was reduced in amount and the chest hair was absent. Spider angiomas were noted about the face and shoulders. The laboratory results were as follows: red blood count 3.5 million; hemoglobin 9.8 gm.; serum bilirubin 12.2 mg. per cent; total protein 5.8 gm. per cent with albumin 2.4 gm. per cent and globulin 3.4 gm. per cent.

On the first hospital day the patient was nauseated, vomited occasionally, and ate very little. He continued agitated and hallucinatory.

On the second day deep coma developed; however, he would respond slightly to painful stimuli and nuchal rigidity was noted. In addition to general therapeutic and supportive measures the patient was given adrenal cortical extract during the initial twenty-four-hour period. On the third day the patient became more alert and took small amounts of food by mouth. Intravenous feedings were continued. Three days later he again lapsed into stupor and began hallucinating. On the seventh day the serum potassium was found to be 2.3 mEq. per cent. Potassium replacement in the amount of 112 mEq. of oral potassium daily was begun and was continued for thirty days. Twenty-four hours following the institution of potassium replacement the patient became rational. During this period serial electrocardiograms demonstrated prolongation of the Q-T interval and flattening and broadening of the T wave. With return of potassium serum levels to normal, further electrocardiograms were not taken.

By mid-December, 1951, there had been partial return of liver function studies toward normal and the patient continued to feel well. (Fig. 3.)

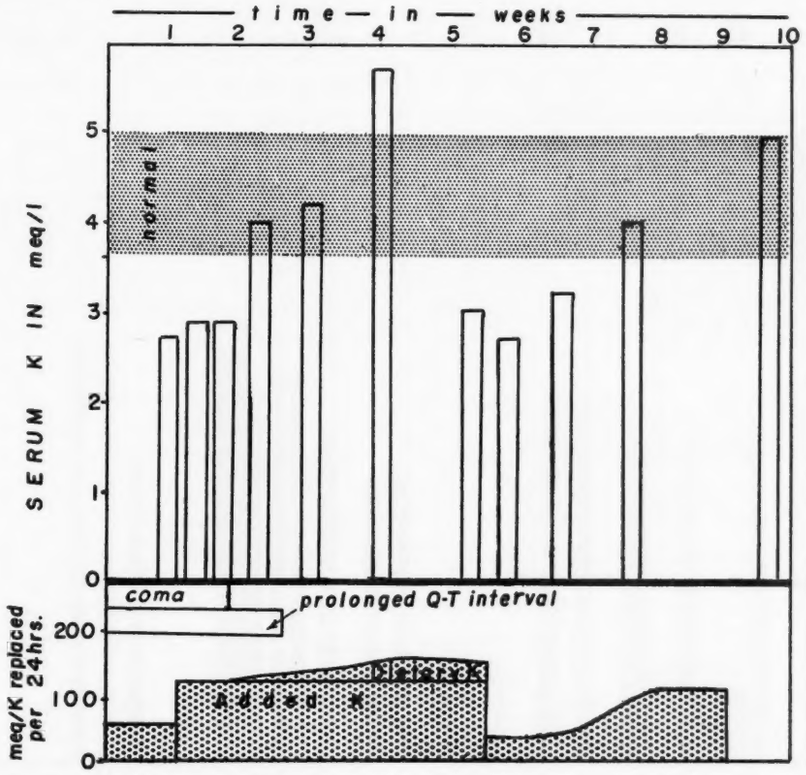


FIG. 3. Case O. B. The stippled area labeled added K represents oral as well as intravenous potassium salts.

CASE IV. A. F., a fifty-six-year old civil engineer and long-standing alcoholic, was admitted on May 21, 1951, complaining of loss of 20 pounds of weight, increasing fatigue, enlargement of the abdomen, swelling of the legs, vomiting two or three times weekly, and intermittent, watery, bloodless diarrhea since January, 1951. Two abdominal paracenteses had been done five and three weeks earlier. On admission the patient was a small, malnourished, slightly icteric, febrile, white man with ruby red lips and tongue. There was hepatomegaly and ascites. The axillary and pubic hair was diminished; chest hair was absent. Spider nevi were present over the face and chest.

The laboratory data were as follows: red blood count, 2.9; hemoglobin 9.1 gm.; white blood count, 8,300. Urine: albumin negative; sugar negative; specific gravity 1.005; microscopic 5 to 10 white blood cells and 2 to 3 red blood cells per high power field. Liver function: BSP retention 44 per cent in thirty minutes; cephalin flocculation test 3+ in twenty-four hours; thymol turbidity test 6.0 McLagan units; total protein 8.5 gm. per cent, with albumin 2.7 gm. per cent and globulin 5.8 gm. per cent; alkaline phos-

phatase 5.7 King-Armstrong units; prothrombin activity 15 per cent. Chemistry: blood urea nitrogen 5.0 mg. per cent; serum calcium 8.1 mg. per cent; inorganic phosphorus 4.4 mg. per cent; total base 139 mEq.; CO_2, 33 mEq./L.

Serial sodium and potassium estimations were made throughout his course. In fifteen electrocardiograms taken approximately weekly throughout the four months, the Q-T interval varied from the upper limits of normal to prolonged. The T waves were on most occasions broadened and flattened. These changes were most pronounced at times when the serum potassium values were lowest. (Fig. 4.)

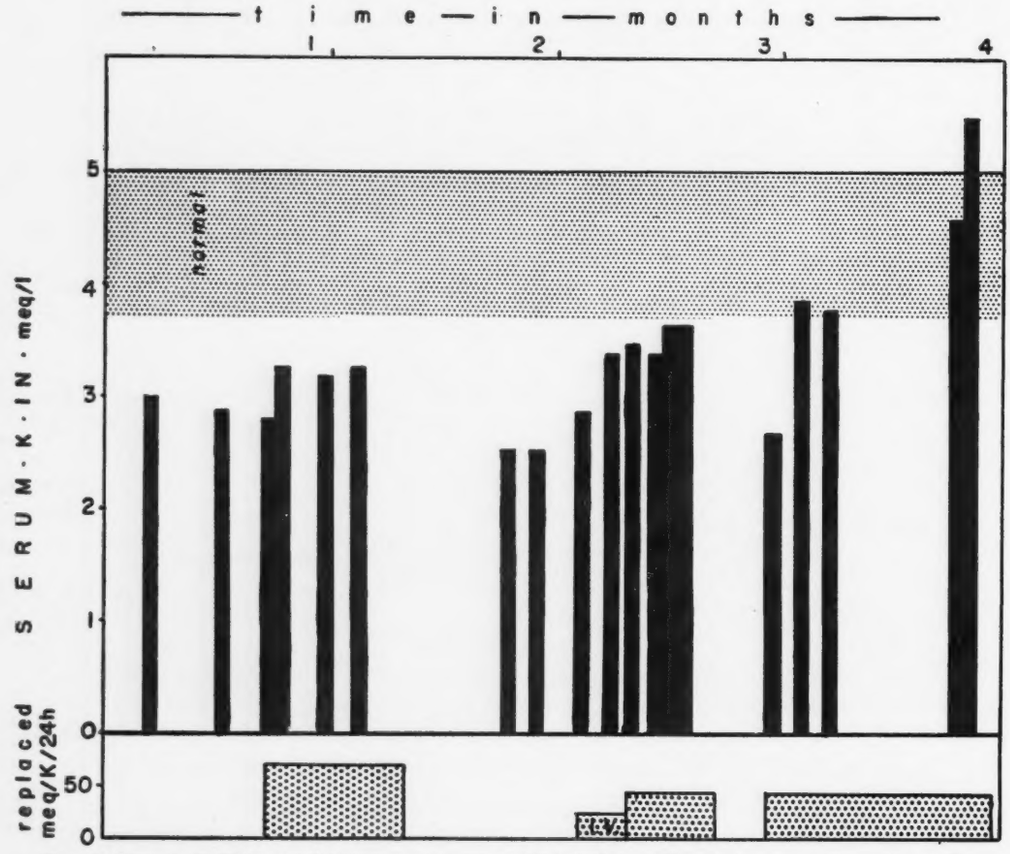


FIG. 4. Case A. F. The stippled area represents added oral as well as intravenous potassium salts.

In spite of the fact that the ascites was reduced with mercurials and low salt diet he continued to deteriorate, eating poorly, remaining lethargic and intermittently disoriented. Three massive hematemeses occurred, one at the end of the second month, another at the end of the third, and a fatal one at the end of the fourth month.

CASE V. H. H., a white fifty-three year old alcoholic of many years with bilateral pulmonary tuberculosis, who had been drinking whiskey and eating very little for several months, was admitted in extremis due to congestive heart failure and malnutrition. On a previous admission, Laennec's cirrhosis had been demonstrated by punch biopsy. On physical examination he was unkempt, slightly disoriented, cyanotic and orthopenic. Blood pressure was 110/70, temperature 99°F., and pulse 110. There was 4+ pretibial edema. Both lung fields were filled with moist and bubbling rales. Hepatomegaly and slight ascites were present. The axillary and pubic hair was scant and the chest hair was absent. The genitalia were atrophic and spider angiomas were noted about the face and shoulders. No icterus was visible.

The admission laboratory data were as follows: red blood count, 3.0; hemoglobin 12.2 gm.; hematocrit 40.5; cephalin flocculation test 3+; thymol turbidity test 6; serum bilirubin 0.4 mg. per cent; total protein 5.6 per cent, with

albumin 2.6 gm. per cent and globulin 3.0 gm.; total base 125 mEq./L.; prothrombin time 100 per cent; BSP retention 14 per cent; sputum positive for acid-fast bacilli. The chest x-ray demonstrated advanced fibrotic disease in both lung fields. The electrocardiogram was abnormal with prolongation of the Q-T interval and broadening and flattening of the T waves.

Mercurial diuretics were administered on the first and second days and digitalization was completed on the third day. In this period 15 pounds of weight were lost by diuresis. Food and fluid intake were poor and there was occasional vomiting. The patient became stuporous and hallucinatory. There was marked loss of skin turgor.

Serum electrolyte values on the third hospital day were as follows: Potassium 2.3 mEq./L.; sodium 128 mEq./L.; total base 129 mEq./L.; total protein 6.3 gm. per 100 cc.

Replacement therapy was begun on the third hospital day. This consisted of Ringer's solution, glucose, two whole blood transfusions, parenteral vitamin B complex, lipo-adrenal extract and added potassium in the amount of 100 mEq. per day for nine days. The patient was in coma for forty-eight hours. This was followed by a four-day period during which the patient was boisterous and unruly. There was marked muscular weakness and subjective difficulty in breathing which persisted until normal potassium values were attained. The Q-T interval remained prolonged until the thirteenth hospital day. Figure 5 summarizes the relationship of potassium intake to serum electrolyte levels over a period of two weeks.

Case VI. B. S., a forty-four year old white chronic alcoholic, was admitted July 17, 1951, because of abdominal swelling and shortness of breath. He had suffered from abdominal discomfort and nausea intermittently for two years. Examination revealed florid facies with dilated vessels and slight icterus. There was marked ascites. On admission abdominal paracentesis removed 4,550 cc. of fluid and the liver was then found to be palpably enlarged to 7 cm. below the right mid-costal margin and was non-tender.

Laboratory data early on admission: white blood count, 13,700; red blood count, 2.2; hemoglobin 7.0 gm.; serum sodium 123 mEq./L.; serum potassium 4.6 mEq./L.; chlorides 85 mEq./L.; CO_2, 39 mEq./L.; prothrombin activity 20 per cent; BSP retention 59 per cent retention in thirty minutes; alkaline phosphatase 4.4 King-Armstrong units; cephalin flocculation test 1+; serum bilirubin 11 mg. per cent; thymol turbidity test 4 McLagan units; total protein 7.8 gm. per cent, with albumin 2.8 gm. per cent and globulin 5.0 gm. per cent.

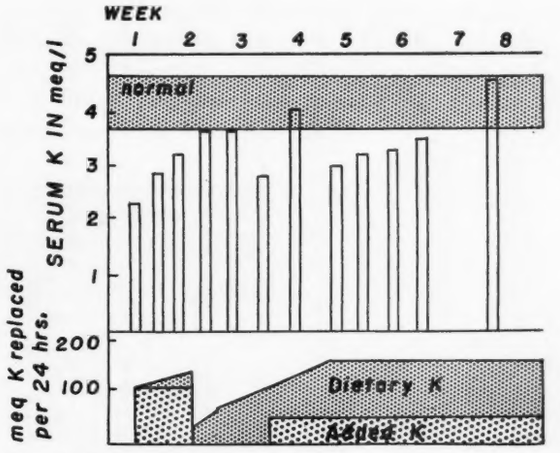


Fig. 5. Case H. H. The stippled area labeled added K represents oral as well as intravenous potassium salts.

Two days after admission the patient became loud, confused, overactive, hallucinating and was moved to the psychiatric ward. Sodium amytal and paraldehyde were used to control overactivity and there ensued a comatose state from which he could not be aroused.

Because it was believed that coma was the result of oversedation in a delirium tremens case, ACTH and cortone were given for two days and on the twentieth he was alert, clear mentally and eating. Liquid stools were noted and continued for several days.

The hepatic regimen outlined above was instituted on July 23, 1951. Serum potassium levels were 4.3 and 4.6 mEq./L. on admission but by the sixteenth day were observed to be 2.7 mEq./L. On the nineteenth day 32 mEq. daily of oral potassium were added to the diet and was repeated daily until the sixty-third hospital day. Because of persistent ascites a cation exchange resin was started on the forty-third day and continued until the sixty-ninth hospital day. It is interesting to note that no further significant change in serum potassium occurred. Serum potassium levels remained in the low normal range after the twenty-sixth hospital day. Prothrombin values remained low throughout the hospital course.

In Figure 6 it is interesting to note that the serum potassium was normal during the period of coma. This would support our impression that excessive barbiturates had been used. The gradual fall of potassium over a two-week period was thought to be due to a combination of factors, i.e., anorexia, diarrhea, paracentesis and the use of mercurial diuretics.

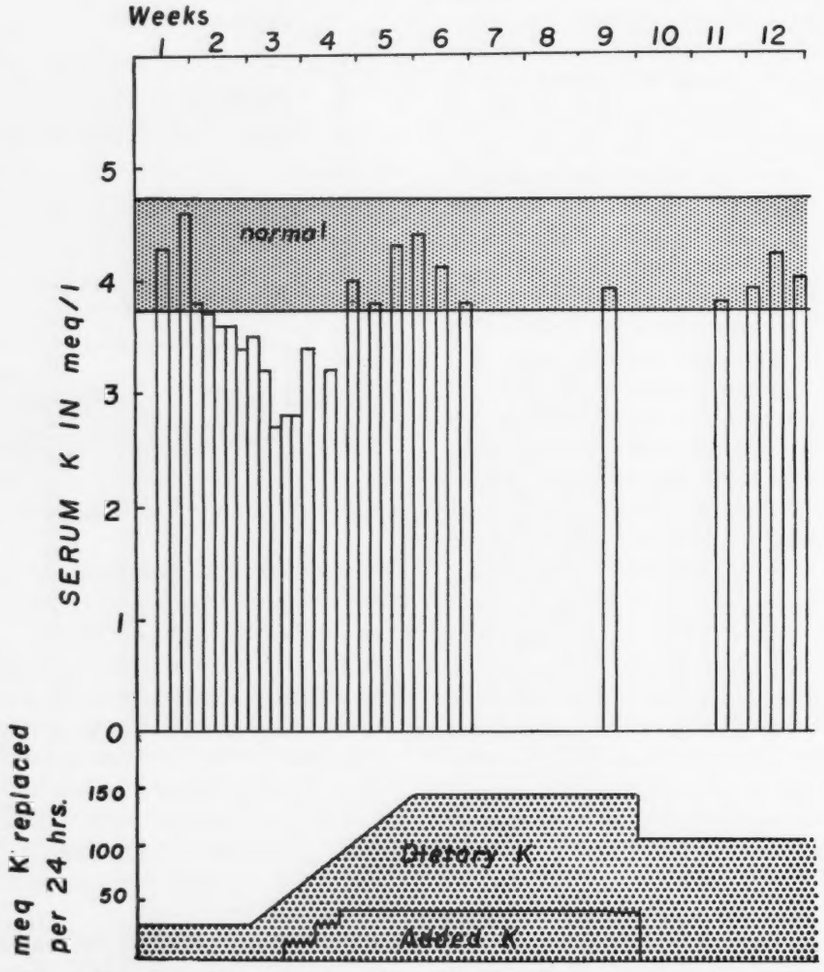


FIG. 6. Case B. S. The stippled area labeled added K represents oral as well as intravenous potassium salts.

COMMENT

Both cirrhosis of the liver and potassium depletion states are well known to be associated with poor dietary habits. Poor appetite, nausea, decreased food intake, diarrhea and vomiting are common in cirrhosis and may separately or in combination cause loss of potassium. Vomiting may account for losses of 5.0 to 7.0 mEq. of potassium per L. of vomitus. There is a negative nitrogen balance[9] in liver cell failure which may persist for long periods and, with each gram of negative nitrogen balance, 2 to 3 mEq. of potassium are lost in the urine. During the starvation period glycogen is mobilized, with transfer of potassium to the serum, and may subsequently be lossed in the urine. Diarrhea, a frequent finding in severe hepatocellular damage, may further potassium loss. Usually this catabolic state exists for long periods before hospitalization and much of the body total potassium may be seriously depleted.

The time-honored and effective treatment consists of giving large quantities of carbohydrates and particularly of glucose intravenously. Glucose loading is well known to lower potassium, apparently because potassium is necessary in glycogen formation and is withdrawn from extracellular reserves during accelerated carbohydrate metabolism. With intracellular potas-

sium reserves already depleted in the debilitated cirrhotic patient, the return of eating, the tendency to positive nitrogen balance, and the consequent increased cellular needs for potassium may also lower serum potassium levels. In the cirrhotic patient these effects can coincide during therapy and may account for low potassium values during a period of clinical recovery (Case II).

Our studies further indicate that there is often severe dehydration with decrease in total base, sodium, calcium and phosphorus as well as potassium. As these are treated with fluids and electrolytes, but with exclusion of potassium, there may be dilution of the potassium in the serum with further lowering of this ion. Often mercurial diuretics are used to treat ascites and again potassium is lost.

Low potassium can contribute to death in many critical states by producing altered function as well as necrosis of skeletal and cardiac muscle.[10] Clinically one may observe muscular weakness, including respiratory muscle weakness, constipation, bladder atony, prolonged Q-T or P-R intervals, broadened flat T waves, cardiac enlargement, arrhythmia and congestive failure.

Our cases represent a pilot series of observations rather than a controlled study of metabolism in cirrhosis. Therefore it would be hazardous to draw any conclusions. However, we do believe that the findings set forth serve to emphasize a situation which has heretofore been mentioned as an incidental finding in only a few cases of acute hepatic failure in cirrhosis, namely, hypokalemia. Although we cannot at this time exactly define the importance of potassium replacement as related to recovery from hepatic failure, we have formed a strong clinical impression that restoration of depleted stores of body potassium may often be of critical importance.

CONCLUSIONS

1. Twenty-five of the thirty cases of cirrhosis of liver in hepatocellular failure constituting this study showed hypopotassemia either on admission or early in the recovery phase. The more severe the manifestations of cirrhosis and the more prolonged the period of malnutrition the greater appeared to be the likelihood of hypokalemia and lowered total body potassium.

2. Eight of ten cases of hepatic coma recovered on a regimen including added potassium ion as replacement therapy. This may have contributed to the high percentage of recovery.

3. Some of the theoretic causes of hypopotassemia in cirrhosis are discussed.

REFERENCES

1. Snell, A. M. and Butt, H. R. Hepatic coma: observations bearing on its nature and treatment. *Tr. A. Am. Physicians*, 26: 321–329, 1941.
2. Eisenmenger, W. J., Blondheim, S. H., Bongiovanni, A. M. and Kunkel, H. G. Electrolyte studies on patients with cirrhosis of the liver. *J. Clin. Investigation*, 29: 1491–1499, 1950.
3. Latner, A. L. Regime for treatment of severe and acute liver disease. *Brit. M. J.*, 2: 748–751, 1950.
4. Farber, S. J., Pellegrino, E. D., Conan, N. J. and Earle, D. P. Observations on the plasma potassium level of man. *Am. J. M. Sc.*, 221: 678–687, 1951.
5. Bodansky, O. Recent advances in parenteral fluid therapy with ammonium chloride and potassium. *Am. J. M. Sc.*, 218: 567–586, 1949.
6. Martin, H. E., Reynolds, T. B., Snyder, E. N., Berne, C. J., Homann, R. E., Jr., Edmondson, H. A., Blatherwick, N., Fields, I., Wertman, M. and Westover, L. Etiology and treatment of serum potassium deficits. *J. A. M. A.*, 147: 24–30, 1951.
7. Danowski, T. S. Newer concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525–531, 1949.
8. Amatuzio, D. S., Stutzman, F., Shrifter, N. and Nesbitt, S. A study of serum electrolytes (Na, K, Ca, P) in patients with severely decompensated portal cirrhosis of the liver. *J. Lab. & Clin. Med.*, 39: 26–29, 1952.
9. Cook, W. R. and Van Auken, H. A. Nitrogen balance studies in Laennec's cirrhosis of the liver. *Ann. Int. Med.*, 34: 1404–1415, 1951.
10. Danowski, T. S., Greenman, L., Peters, J. H., Mateer, F. M., Weigand, F. A. and Tarail, R. The use of cation exchange resins in clinical situations. *Ann. Int. Med.*, 35: 529–541, 1951.

Pulmonary Function in Sarcoidosis*

Results with Cortisone Therapy

DANIEL J. STONE, M.D., ARTHUR SCHWARTZ, M.D., JAMES A. FELTMAN, M.D. *and* FRANCIS J. LOVELOCK, M.D.

with the technical assistance of Mrs. Blanche Devlin

New York, New York

PULMONARY sarcoidosis has for years been considered for the most part a benign disease functionally, characterized by mild ventilatory insufficiency with slight to moderate reduction of lung volumes.[1] There have been sporadic reports of severe functional disability with cor pulmonale in this disease.[2] Spain[3] has commented upon the tendency for sarcoid lesions to assume a peribronchial distribution with resultant peribronchial fibrosis and emphysema. In a recent review of the subject Longcope and Freiman[4] gave a complete account of the pathologic processes in this disease and commented upon the serious functional disability that may result. Although there have been several small series of function studies reported,[5,6] there has been no attempt to correlate the functional picture with the duration and stage of the disease and the clinical findings at the time of study.

The purpose of this paper is: (1) to report the results of pulmonary function studies in an unselected group of patients with sarcoidosis; (2) to correlate the functional pattern with the clinical picture in various stages of the disease; and (3) to analyze the effect of cortisone and ACTH therapy on pulmonary function.

MATERIAL AND METHODS

The study of twenty-two male patients with sarcoidosis forms the basis of this report. These represent all available cases observed at this hospital over a six-year period. For purposes of tabulation and discussion these cases have been divided into three groups. Group I consists of cases which were known to have had active pulmonary sarcoidosis at least three years prior to study. Group II consists of those with recent onset of acute symptoms and pulmonary disease. The majority of these patients were studied consecutively during a two and one-half-year period and were treated, without selection, with cortisone or ACTH. Group III includes those patients with proved sarcoidosis without clinical or radiographic evidence of pulmonary involvement.

In all cases, with the two exceptions noted in Table I, the diagnosis of sarcoidosis was proved histologically by tissue biopsy or positive Kveim reaction. The two unproved cases (Cases 4 and 6) are included because of a characteristic clinical picture. The criteria for diagnosis were essentially those established in earlier studies.[7,8] The details of cortisone therapy and the clinical effects are reported elsewhere.[9]

Pulmonary function studies were performed on each patient using the technics as outlined by Baldwin et al.[10] for lung volumes, ventilation, exercise response, maximum breathing capacity and blood gases. The analyses of gas tensions and calculation of the alveolar-arterial oxygen gradients on room air and low oxygen mixtures (12 to 16 per cent O_2) were performed by the technics described by Lilienthal and Riley, and others.[11] The approximate percentage of venous admixture and the diffusing capacity were calculated in several cases in an attempt to analyze the A-A gradient in accord with the theoretical considerations of Riley and others[12–14] and are included where pertinent. Analysis of expired air for carbon dioxide and oxygen was performed on the micro-Scholander apparatus. Where the respiratory quotient was elevated or there was other evidence of a non-basal or unsteady state, the study was repeated before inclusion in the report. In most cases

* From the Medical Service and Cardiopulmonary Laboratory of the Bronx Veterans Administration Hospital, New York, N. Y.

TABLE I

CLINICAL AND X-RAY DATA

Group I

Case No.

1. 32W. Diffuse, nodular pulmonary infiltrates, hilar and mediastinal adenopathy, positive node biopsy nine years before study; chest x-ray at time of study showed fine linear fibrosis; mild effort dyspnea two years.
2. 45W. Bilateral root nodal enlargement with obstruction of right middle lobe bronchus; right middle lobe lobectomy five years before studies—lung and nodes positive for sarcoid; patient asymptomatic and x-rays clear since surgery.
3. 30N. Acute onset with dyspnea and wheezing four years before studies; endobronchial lesion, diffuse pulmonary disease and generalized adenopathy noted; partial spontaneous regression one year later; chest x-ray at time of study showed fine, diffuse, reticular infiltrate and moderate emphysema; no adenopathy.
4. 32W. Stationary, bilateral confluent densities observed four years; dyspnea one year; diagnosed on clinical basis, no biopsy.
5. 61W. Peripheral node biopsy positive six years before studies; episode of cor pulmonale with cardiac decompensation five years later; dyspneic at rest; chest x-ray at time of study showed confluent, diffuse linear lesions radiating from the hila, with emphysema and cardiac enlargement.
6. 28W. Diffuse, granular confluent pulmonary infiltrate with mild symptoms one year prior to first study; slow progression roentgenographically at time of second study, nineteen months later.
7. 36N. Asymptomatic pulmonary infiltrate discovered three years before study; recent dyspnea; chest x-ray at time of first study showed diffuse bilateral infiltrate, moderate root nodal enlargement; no change in three months on bed rest; slight clinical and x-ray improvement following cortisone therapy.

Group II

8. 27W. Recent onset of acute symptoms with dyspnea; chest x-ray showed diffuse reticular infiltrate, mediastinal adenopathy; rapid and complete clinical and x-ray response to cortisone.
9. 28W. Three months' history of acute symptoms with dyspnea; chest x-ray showed diffuse confluent pulmonary infiltrates, massive hilar and mediastinal adenopathy; clinically well, with partial x-ray clearing following cortisone.
10. 25W. Acute onset with dyspnea; chest x-ray showed diffuse confluent pulmonary infiltrates, mediastinal and hilar adenopathy; moderate clinical improvement following cortisone, with x-ray evidence of linear fibrosis.
11. 24W. Gradual onset over one year; chest x-ray showed diffuse confluent pulmonary infiltrate, minimal adenopathy; prompt clinical and x-ray response to cortisone; relapse in two months, retreated with good clinical and roentgenographic response.
12. 39W. Recent onset of cough, dyspnea and wheezing; endobronchial sarcoid proved; chest x-ray showed localized bilateral infiltrates; clinically improved following cortisone, no x-ray change.

TABLE I (*Continued*)

13. 32N. Recent onset with dyspnea; diffuse reticular infiltrate noted on chest x-ray; partial clinical and x-ray response to ACTH; development of progressive dyspnea.
14. 22W. Acute onset with dyspnea; chest x-ray showed diffuse confluentin filtrate, moderate hilar adenopathy.
15. 25W. Recent acute onset; chest x-ray showed diffuse fine nodular densities, marked hilar adenopathy.
16. 45N. Recent onset with severe dyspnea; chest x-ray showed fine, stippled infiltrate throughout both lung fields.

Group III

17. 33W. Marked root nodal enlargement, stationary for four years; asymptomatic.
18. 45W. Stationary root nodal disease five years; slight dyspnea.
19. 27N. Mediastinal and root nodal enlargement of recent origin; slight dyspnea.
20. 29W. Acute onset with erythema nodosum; prominent hilar nodes, minimal, streaky right upper lobe infiltrate.
21. 26N. Long-standing (seven years) nodal, skin and finger involvement; chest x-ray showed moderate root and paratracheal node enlargement; no change in x-ray following cortisone.
22. 32W. Recurrent peripheral adenopathy five years; minimal root nodal enlargement.

direct pH measurements of the arterial blood were performed with the Cambridge Research pH meter. Calculated tensions of carbon dioxide were obtained utilizing the Henderson-Hasselbalch equation.[15] The correlation between the calculated pCO_2 and the directly measured result, utilizing the bubble technic, was sufficiently close to minimize any error in the gradient calculations.

RESULTS AND COMMENTS

Group I. In cases with known pulmonary parenchymal involvement of at least three years' duration the following functional patterns were observed (Tables II and III):

A. *Emphysema pattern* (Cases 3, 5 and 6): (1) Significant elevation of residual air and alveolar nitrogen; reduced vital capacity and total lung volume. (2) Significant reduction of maximum breathing capacity. (3) Spirographic evidence of obstruction. (4) In two of the three cases (3 and 5) there was noted arterial oxygen unsaturation at rest and with exercise. There was an elevated alveolar-arterial oxygen gradient on breathing room air in all three, and elevated gradients in two (Cases 5 and 6) on breathing low oxygen mixtures. The calculated diffusing capacities and venous admixtures in these cases indicate combined venous admixture and dif-

TABLE II

LUNG VOLUMES AND VENTILATION

Case	Lung Volumes (% of predicted)			RA/TC × 100	Alveolar N_2	Maximum Breathing Capacity (% of predicted)	Ventilation—L./min./sq. m.		
	Vital Capacity	Residual Air	Total Capacity				Basal	Exercise	1st min. Recovery
Normal	100	100	100	<30	<2.5	100	<4.0	<10.0	<12.0
Group I									
1. 9 Years after onset of disease	100	72	90	15.9	1.74	64	3.98	9.75	13.7
2. 5 Years after lobectomy; no clinical disease at time of study	89	106	96	27.0	2.20	100	5.76	14.6	16.1
3. 4 Years after onset of disease	48	155	74	41.3	4.54	57	4.67	7.75	11.6
4. 4 + Years after onset of disease	56	97	66	29.1	1.62	49	3.72	11.2	16.8
5. 6 + Years of known pulmonary disease	66	158	90	42.8	4.74	65	4.23	12.5	12.0
6. (a) Pulmonary lesions one year	72	125	86	28.8	2.33	89	2.93	13.9	....
(b) 19 Months later—no treatment	59	159	82	38.5	2.70	68	3.87	7.78	8.88
7. (a) 3 Years after appearance of pulmonary lesions	76	87	78	27.1	1.76	121	4.66	7.65	12.6
(b) 3 Months later—no treatment	70	81	72	27.3	2.45	107	4.80	7.94	12.6
(c) Following cortisone therapy	76	67	70	23.2	1.75	128	6.10	10.0	17.0
Group II									
8. (a) Control study	85	104	86	24.0	1.70	95	4.64	18.3	26.5
(b) 6th Week of cortisone therapy	91	...	...	....	....	109	3.26	9.17	15.0
(c) 1 Year after completion of therapy	97	111	101	21.6	2.45	101	2.90	9.67	13.5
9. (a) Control study	75	95	80	23.6	1.42	123	4.41	16.6	16.3
(b) 4 Weeks after completion of therapy	71	66	72	18.2	1.89	126	3.97	11.0	14.1
(c) 11 Months after completion of therapy	80	77	80	19.0	1.87	159	3.73	8.80	10.9
10. (a) Control study	46	81	53	30.5	1.86	73	5.04	17.7	20.3
(b) Immediately after completion of therapy	59	58	59	19.5	2.32	85	4.06	13.1	17.3
(c) 7 Months after completion of therapy	60	66	62	20.8	3.05	85	4.02	11.6	12.8
11. (a) Control study	64	97	68	28.4	1.87	104	4.91	16.8	17.4
(b) Clinical exacerbation—6 weeks after completion of first course of therapy	71	89	74	23.9	1.70	101	6.18	12.1	15.8
(c) Following second course of therapy	82	94	83	22.4	1.70	109	4.18	9.97	12.4
12. (a) Control study	106	115	107	26.2	3.42	41	4.40	11.3	....
(b) Immediately after completion of therapy	101	123	106	29.2	2.09	71	3.80	11.5	16.5
13. (a) Control study	51	110	62	34.9	3.91	52	6.30	15.7	17.5
(b) 3 Weeks after completion of ACTH therapy	55	80	58	27.2	2.40	69	4.95	15.1	16.9
(c) 5 Months after completion of ACTH therapy	40	129	60	42.4	3.40	57	5.70	17.45	20.0
14. Initial study	55	50	55	18.0	1.19	80	4.62	15.0	18.8
15. Initial study	83	74	84	17.7	3.13	100	5.46	12.0	15.0
16. Initial study	54	58	62	22.8	3.05	120	6.93	15.45	23.6
Group III									
17. Root nodal disease—4 + years	114	112	109	20.3	2.15	104	4.28	11.45	10.75
18. Root nodal disease—5 years	98	91	101	21.9	2.80	86	3.96	12.5	16.0
19. Root nodal disease—recent	109	93	102	18.1	1.45	95	5.26	12.9	15.4
20. Root nodal disease—recent	104	111	112	19.7	1.46	168	4.56	19.6	22.7
21. (a) Root nodal disease—7 + years	79	67	79	16.8	1.64	108	4.48	13.6	11.5
(b) 3rd Month of cortisone therapy	83	65	79	16.2	1.43	109	4.75	10.2	10.4
22. Peripheral adenopathy, ? root nodal disease	80	79	79	19.9	1.98	92	3.37	8.77	11.6

TABLE III

OXYGEN CONSUMPTION AND GAS STUDIES

Case	O_2 Consumption (cc./min./sq.m.)		O_2 Saturation %			CO_2 Content (vol. %)	Room Air					Low Oxygen					V.A. % C.O.*	DO_2†
	Basal	Exercise	Basal	Exercise	Low O_2		Arterial pCO_2	Alveolar pO_2	Arterial pO_2	A-A Grad.	Dead Space	Arterial pCO_2	Alveolar pO_2	Arterial pO_2	A-A Grad.	Dead Space		
							(mm. Hg)		(mm. Hg)		(% T.A.)	(mm. Hg)		(mm. Hg)		(% T.A.)		
Normal	129 ± 13	480 ± 74	96 ± 2	96 ± 2	....	48 ± 4	35–40	100	90–100	<12	<30%	35–40	..	..	<12	<30	<6	>15
Group I																		
1.	143	481	95.0	94.8	76.4	45.1	42	98	93	5	31	39	39	38	1	32	3	....
2.	199	662	95.3	95.9	81.4	47.9	38	103	86	17	28	33	59	46	13	33	8	16.7
3.	127	339	91.4	88.5	79.7	50.7	45	97	78	19	43	42	54	43	11	42	12	14.5
4.	109	410	98.4	93.0	....	45.6	44	97	98	−1	36	..	..	..	..	..	...	....
5.	147	346	89.0	88.4	67.4	49.7	44	94	61	33	34	42	52	30	22	32	18	8.8
6. (a)	107	498	96.0	99.0	....	43.1	42	99	96	3	..	..	..	..	..	..	1.5	....
(b)	119	299	94.0	93.5	83.3	42.5	35	108	81	27	29	32	66	46	20	33	13	9.4
7. (a)	160	375	93.7	92.5	78.6	44.2	43	95	86	9	37	42	53	44	9	39	5.5	20.2
(b)	164	398	92.5	88.5	81.7	40.9	42	96	82	14	37	37	61	52	9	34	8	17.2
(c)	186	437	91.7	82.6	73.4	45.3	42	95	82	13	30	44	53	47	6	35	8	29.0
Group II																		
8. (a)	148	450	97.4	99.0	....	44.3	36	111	108	3	23	..	..	..	..	..	...	....
(b)	144	470	96.0	94.8	....	47.0	40	103	105	−2	15	..	..	..	..	..	...	....
(c)	135	606	96.0	....	87.4	44.2	36	103	93	10	11	38	56	59	−3	21	5	....
9. (a)	154	463	94.0	97.7	....	46.5	43	97	88	9	34	..	..	..	..	..	5	....
(b)	133	445	98.5	95.4	....	46.3	38	101	87	14	32	..	..	..	..	..	7	....
(c)	142	395	96.0	96.3	88.3	45.1	38	103	90	13	22	36	60	53	7	21	6	15
10. (a)	137	554	95.5	91.7	....	48.0	40	106	92	14	35	..	..	..	..	..	6	....
(b)	123	446	92.7	86.7	88.5	43.0	42	102	88	14	35	42	59	56	3	40	7	....
(c)	131	491	92.3	86.1	82.7	44.2	43	98	75	23	30	37	60	57	3	31	15	....
11. (a)	162	537	96.6	93.3	89.0	45.4	46	94	86	8	38	50	49	57	−8	41	4	....
(b)	170	482	94.3	90.3	88.7	47.5	43	96	90	6	42	42	55	50	5	43	3	30
(c)	130	467	96.5	94.0	91.0	49.3	34	111	107	4	17	39	60	64	−4	29	2	....
12. (a)	146	474	....	....	....	....	..	...	..	..	..	..	..	..	..	..	...	....
(b)	130	433	95.3	96.3	....	49.0	39	102	96	6	24	..	..	..	..	..	3	....
13. (a)	169	428	94.4	92.0	79.8	44.2	44	95	77	18	48	43	54	46	8	50	12	25.0
(b)	142	494	94.5	88.2	83.9	46.0	38	104	82	22	38	38	61	45	16	39	12	13.7
(c)	149	420	91.4	91.5	83.7	39.0	34	107	71	36	37	33	73	53	20	34	...	....
14.	171	547	96.7	95.8	....	48.1	47	90	86	4	37	..	..	..	..	..	2	....
15.	157	473	99.5	90.7	72.5	43.7	37	106	96	10	35	37	39	37	2	47	3	....
16.	143	323	87.7	79.9	77.3	35.7	34	106	72	34	42	30	72	44	28	41	20	7.5
Group III																		
17.	143	497	94.3	95.1	81.0	49.7	39	100	84	16	32	36	60	55	5	29	8	21.8
18.	134	565	94.0	95.4	83.5	41.7	36	105	82	23	24	33	64	55	9	20	12	14.5
19.	155	559	97.6	95.8	76.6	38.3	35	108	100	8	31	40	38	37	1	34	2	....
20.	147	636	95.8	94.8	....	50.3	44	97	87	10	34	..	..	..	..	..	4	....
21. (a)	147	428	96.4	97.5	83.7	49.3	40	104	95	9	27	40	58	57	1	26	3	....
(b)	158	461	94.0	91.7	79.3	48.3	45	92	89	3	38	44	52	51	1	35	1	....
22.	115	434	95.7	94.3	83.8	45.0	36	107	95	12	16	36	60	64	−4	18	5	....

* Venous admixture in percentage of cardiac output.

† Diffusing capacity in cc. of O_2 consumed/unit time per mm. Hg of mean alveolar capillary oxygen gradient.

fusion abnormalities. While the low diffusing capacities may possibly represent an alveolocapillary block,[16] it would seem more probable that this finding is related to loss of total diffusing surface secondary to severe emphysema.

B. *Fibrosis pattern* (Cases 1, 4 and 7): (1) Variable degrees of reduction in all lung volumes and maximum breathing capacity without evidence of emphysema. (2) No significant abnormalities in gas exchange except for arterial oxygen unsaturation with exercise noted in one study in Case 7.

In this entire group only one patient (Case 2) had essentially normal pulmonary function.

This patient at no time had evidence of generalized lung involvement. (Table I.) The development in nineteen months of significant emphysema in Case 6 is striking. Fluoroscopic and clinical evidence of mild emphysema was also noted after the beginning of regression of parenchymal disease in Case 3, and in this patient significant functional impairment was already present one year later.

Group II. Observations in cases with diffuse pulmonary involvement of recent origin are tabulated in Tables II and III (Cases 8–16). The clinical pictures are described in Table I. The following features were noted:

1. There was significant reduction of vital and total capacity in all cases except one (Case 12). The residual volume was either normal or reduced in all cases, and there was no evidence of emphysema. There was no spirographic evidence of bronchial obstruction, with the exception of Case 12 who also demonstrated bronchoscopic evidence of sarcoidosis. Those cases with reduction in all lung volumes resemble the fibrosis pattern seen in group I.

2. The maximum breathing capacities demonstrated no constant trend. There was moderate reduction in four cases. Hyperventilation at rest, with exercise and recovery, was a constant and striking feature of this group of cases. In general these patients were more dyspneic than those in groups I and III.

3. Gas exchange was impaired on initial study in five of the cases in this group. Four of these had slight decrease in arterial O_2 saturation with exercise; one (Case 16) had marked unsaturation at rest and with exercise. This case demonstrated a definite alveolo-capillary block pattern[16] as manifested by high A-A gradient on breathing a low oxygen mixture, a reduced oxygen consumption with exercise and elevated dead space measurements with a low arterial pCO_2. Significant gradients on breathing room air were noted in two cases; borderline elevation of gradients were present in two others. Inconstant elevations of physiologic dead space and arterial pCO_2 were noted.

Group III. Observations in this heterogeneous group of six cases without clinical evidence of pulmonary disease revealed the following significant findings: (1) Lung volumes were normal in four patients and significantly reduced in all compartments in two. In the latter two cases the over-all functional picture was thus similar to the three patients in Group I with x-ray evidence of long-standing fibrosis. (2) Maximum breathing capacities were not significantly altered. (3) Hyperventilation with exercise and recovery was noted in three cases. One of these, an acute case with erythema nodosum, demonstrated hyperventilation responses of the same magnitude as the patients in group II. (4) There were minor abnormalities of ventilation-perfusion relationships as demonstrated by elevated room air gradients in two patients, indicating increased venous admixtures.

SERIAL OBSERVATIONS OF THE EFFECTS OF CORTISONE AND ACTH

Acute Recent Cases. Case 8: Complete restoration of lung volumes to normal and return of ventilatory responses to more normal levels were noted after six weeks of therapy. Improvement was maintained at the time of the final study one year later. Gas exchange remained normal throughout the entire period of observation. Complete relief of dyspnea was striking.

Case 9: The lung volumes were relatively unchanged except for an early decrease in residual air which was maintained eleven months later. Hyperventilation was less apparent and dyspnea was absent following therapy. At no time were abnormalities of gas exchange noted.

Case 10: Lung volumes demonstrated a significant reduction in residual air following therapy. Ventilation responses returned to normal and the patient was less dyspneic. Gas exchange studies following cortisone therapy revealed further evidence of anoxia as shown by the appearance of arterial oxygen unsaturation at rest and the further decrease in exercise oxygen saturation. The increased venous admixture is indicated by increase in the room air gradient.*

Case 11: Improvement in the vital capacity and total capacity was noted following the second course of cortisone therapy. Ventilation responses returned to normal. An improvement in over-all ventilation-perfusion relationships was demonstrated by decrease in dead space and pCO_2 measurements and return of arterial O_2 saturation to normal.

Case 12: Lung volumes remained normal; the maximum breathing capacity was significantly improved as was the dyspnea. There was clinical

* This patient was restudied fifteen months after the last reported study and this revealed significant improvement in the arterial oxygen saturation with exercise. Moderate elevation of the residual air was noted for the first time.

evidence of diminished bronchial obstruction, probably accounting for the improvement in maximum breathing capacity. Gas exchange studies were normal at the completion of therapy.

Case 13: No improvement in lung volumes was noted and there was significant reduction of residual air immediately following ACTH therapy. Hyperventilation was not affected. Gas exchange and ventilation-perfusion measurements revealed further decrease in exercise arterial-oxygen saturation and the appearance of a diffusion gradient. On restudy five months after completion of ACTH therapy there was definite evidence functionally of interference with gas exchange and the pattern suggested primarily an "alveolo-capillary block."[16] In addition, some functional and fluoroscopic evidence of bronchial obstruction and emphysema was noted for the first time.*

Long-standing Case. Case 7: There was progressive diminution in residual air with no significant change in other lung volumes. Hyperventilation at rest and with recovery from exercise appeared following cortisone therapy. A progressive anoxia is reflected in the decreased rest and exercise O_2 saturation. The worsening of pulmonary function occurred despite x-ray and clinical evidence of improvement.†

Group III Case. Case 21: The only significant changes following cortisone therapy were a decreased oxygen saturation with exercise, increase in dead space and pCO_2, indicating abnormalities of alveolar ventilation. The changes were not striking.

OBSERVATIONS

The observations reported here indicate that regardless of the stage of the disease pulmonary sarcoidosis is associated with a significant degree of functional abnormality. Despite the individual variations described, distinctive features of functional abnormality are found at different chronologic stages of the disease.

The chief functional abnormality in the group of cases of acute pulmonary sarcoidosis of recent origin (group II) is a striking hyperventilation response, especially to exercise. This occurred, with the exception of Case 16, in the absence of significant arterial anoxia or carbon dioxide retention. This type of hyperventilation response occurring in the absence of an abnormal chemical stimulus has long been attributed to the effects of the inflammatory processes on the pulmonary stretch reflexes in the lungs. A similar ventilation response has been noted in acute cases of miliary tuberculosis.[17] It is therefore improbable that this represents a specific pattern in sarcoidosis. With cortisone therapy there was a gradual and significant return of ventilation responses to normal levels. This was associated in all cases with almost complete relief of dyspnea and the majority of these cases showed x-ray clearing as well. It is reasonable to assume that the suppression of tissue inflammation has removed the stimulus for hyperventilation.

The variations in functional responses in the cortisone-treated cases can be explained by fundamental differences in the pathologic processes. In those cases in which cortisone effected a return of lung volumes to normal it must be assumed that the initial reductions were related to encroachment upon the breathing space by an inflammatory process without significant fibrosis. It has been the experience of this group and others[8] that the sarcoid lesions may remain for many months as simple granuloma without organization. This type of pathologic picture has been demonstrated in peripheral lymph nodes and in lung biopsy specimens.[4] It is of interest that in those cases which improved from a functional standpoint with cortisone therapy there was marked clearing of the infiltrate on x-ray. It is also well known that extensive organization of sarcoid lesions with fibrosis may occur[4] and therefore it is reasonable to suppose that the persistence of reduction in lung volumes noted in several of our acute cases indicates the existence of lesions in all stages of the disease, including fibrosis. This was confirmed in one case (Case 10) prior to cortisone therapy by lung biopsy in which all gradations of pathologic responses ranging from edema to hyaline fibrosis were seen. The presence before treatment of a moderate degree of ventilatory insufficiency in this group of acute cases that did not respond to cortisone therapy is additional evidence that irreversible fibrosis of the lung had spontaneously occurred. Two cases in this group and one in group I (Case 7) demonstrated the rapid appearance of a striking and persistent reduction in residual air with cortisone or ACTH therapy, indicating a greater degree of generalized fibrosis and organization of the lung. As noted previously, Case 13 showed,

* Studies sixteen months after the last reported study revealed no essential change from that study.

† Restudy fifteen months later revealed no change in function from that reported at the time of the last study.

following ACTH therapy, a rapidly developing functional impairment which by its nature suggests very extensive interstitial fibrosis and thickening of the alveolo-capillary membranes. It is possible that the secondary development of emphysema resulted from either overdistention of remaining normal lung tissue or from bronchial obstruction due to peribronchial fibrosis, as will be discussed subsequently. The primary difference between a case such as this and the untreated patient who develops functional impairment (group I) would seem to be the rapidity of fibrosis which occurred in the steroid-treated group. While it is possible that such accelerated fibrosis may occur spontaneously, it is more reasonable to assume that the effects are not coincidental but are related to the therapy. The observation that a dense hyaline fibrosis may appear unusually rapidly in peripheral lymph nodes following cortisone therapy has been made by Siltzbach.[8] There is no reason to suppose that the nature or location of fibrosis in a treated patient will differ from that which develops spontaneously in the untreated patient. It is fair to assume that some of the functional impairment would have been seen in the cortisone group even without therapy, but presumably developing more slowly and insidiously as has been observed in our untreated cases. Until long-term physiologic observation on untreated acute cases are available it will not be possible to know for certain whether cortisone or ACTH therapy has increased the actual incidence of functional disturbances due to fibrosis of the lung.

Studies of gas exchange in the untreated acute cases revealed few abnormalities. The exceptions described above occurred in cases in which the over-all functional picture suggested irreversible fibrosis had occurred despite the recent onset of disease. The alveolo-capillary block pattern[16] of Case 16 is striking and represents a much more severe functional abnormality than the type seen in the other acute cases. The cases previously described in which there was an acceleration of fibrosis with cortisone also demonstrated significant arterial anoxia, especially with exercise, and in some instances definite abnormality of alveolar-arterial oxygen gradients were noted. In Case 13 the decrease in diffusing capacity can be related to the fibrosis and organization which has occurred.

It is apparent that the patients in group I who had diffuse pulmonary sarcoidosis in the past, with x-ray evidence of residual disease at the time of study, had abnormal pulmonary function. It is impossible to estimate from this small group the amount or rapidity of progression of disability in any individual case. It is significant, however, that the only patient who had normal pulmonary function at the time of study did not have diffuse disease but had had a resection of a localized lesion five years previously (Case 2). It is clear that the amount of functional impairment is dependent upon the balance between resolution and organization of the inflammatory lesion. It is also evident that the type of functional abnormality can be related to the location of the organizing process. Thus a generalized organization of parenchyma is the basis for the "fibrosis type pattern" seen in several of our cases. Serious disturbances of function of the alveolo-capillary membrane may also occur in this same group. An equally serious type of disturbance is that which occurs as a result of peribronchial fibrosis.[3] This results in bronchial obstruction and varying degrees of generalized and bulbous emphysema. This process may occur with great rapidity, as observed in two of our cases (Cases 3 and 6). One of these (Case 3) had had a proved endobronchial lesion four years previously. In addition, the results of study in one of the acute cases in group II (Case 12) with proved endobronchial sarcoid indicate an early stage of this functional picture.

The finding of significant functional abnormalities in the group of patients without clinical or x-ray evidence of pulmonary parenchymal disease has been described previously. These observations suggest the presence of pulmonary disease which was unrecognized prior to functional studies. This situation is similar to those cases of healed miliary tuberculosis with normal appearing lungs by x-ray.[17] It is possible that our patients may have had lesions identifiable by x-ray at some time in the past.

Results of cardiac catheterization in this group of patients are not sufficiently detailed for presentation as yet. One can only speculate that in view of the severe type of pulmonary dysfunction seen in some of the long-standing cases, pulmonary artery hypertension of a significant degree is likely to be present, especially with exercise. This lesser circuit hypertension can be significant and lead to right heart failure. Severe cor pulmonale with failure was actually present

in one case (Case 5 in group I). The marked reduction in diffusing capacity of the lungs seen in both the treated and untreated groups suggests that there will be significant pulmonary artery hypertension due to restriction of the pulmonary vascular area. In addition, on theoretical grounds[18,19] one might expect that those patients with significant anoxia on mild exercise will eventually develop pulmonary artery hypertension. It will require prolonged observation before the significance of this in relation to the development of clinical cor pulmonale can be determined.

SUMMARY AND CONCLUSIONS

An analysis of the physiologic abnormalities in a group of twenty-two patients in various chronological stages of pulmonary sarcoidosis is presented. Studies made serially in one group of patients treated with cortisone or ACTH are summarized.

Observations in a group of patients with long-standing generalized pulmonary sarcoidosis indicate that an occasional patient may have very little functional abnormality or at most mild ventilatory insufficiency secondary to a generalized fibrosis. The majority of these patients, however, show more marked functional disturbances secondary to organization of the lung with the resultant development of low-diffusing capacities and/or emphysema. The development of cor pulmonale is to be expected in a few of these cases. A possible relationship between the location of the fibrosis and the nature of the functional disability is pointed out.

Studies of sarcoid patients without radiographic evidence of pulmonary involvement revealed the presence of unsuspected pulmonary parenchymal disease. The functional pattern in these cases was similar to those cases with overt pulmonary fibrosis preceded by x-ray evidence of generalized pulmonary sarcoidosis.

The major defect in function noted in acute cases of pulmonary sarcoidosis is the presence of striking hyperventilation and dyspnea. The majority of these patients had, in addition, reduction of total lung capacity of a significant degree. Five of these patients were found to have abnormalities of gas exchange.

Serial studies of seven patients treated with cortisone reveal complete restoration of function to normal in two patients and partial improvement in one patient. The majority of our patients, however, became worse functionally following therapy. Cortisone probably accelerates the development of pulmonary fibrosis.

It is not possible to predict which patients will benefit from specific therapy, although it is suggested that patients with pre-existing evidence of fibrosis, such as reduced lung volume, do not benefit from cortisone therapy.

It is concluded that the routine use of cortisone or ACTH therapy in pulmonary sarcoidosis is not warranted unless indications other than pulmonary functional abnormalities exist.

Addendum: Since this paper was accepted for publication McClement et al.[20] have described the functional picture in sarcoidosis in a somewhat similar group of patients.

REFERENCES

1. Baldwin, E. De F., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. II. A study of thirty-nine cases of pulmonary fibrosis. *Medicine*, 28: 1, 1949.
2. Zimmerman, I. and Mann, N. Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. *Ann. Int. Med.*, 31: 153, 1949.
3. Spain, D. M. Patterns of pulmonary fibrosis as related to pulmonary function. *Ann. Int. Med.*, 33: 1150, 1950.
4. Longcope, W. T. and Freiman, D. G. A Study of sarcoidosis. *Medicine*, 31: 1, 1952.
5. Coates, E. O. and Comroe, J. H., Jr. Pulmonary function studies in sarcoidosis. *J. Clin. Investigation*, 30: 848, 1951.
6. Small, M. J. Favorable response of sarcoidosis to cortisone treatment. *J. A. M. A.*, 147: 932, 1951.
7. Lovelock, F. J. and Stone, D. J. Cortisone therapy of Boeck's sarcoid. *J. A. M. A.*, 147: 930, 1951.
8. Siltzbach, L. E. Effects of cortisone in sarcoidosis. *Am. J. Med.*, 12: 139, 1952.
9. Lovelock, F. J. and Stone, D. J. The therapy of sarcoidosis. *Am. J. Med.*, 15: 477, 1953.
10. Baldwin, E. De F., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
11. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D. and Franke, R. E. An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am. J. Physiol.*, 147: 199, 1946.
12. Riley, R. L. and Cournand, A. "Ideal" alveolar air and the analysis of ventilation: perfusion relationships in the lungs. *J. Appl. Physiol.*, 1: 825, 1948–1949.
13. Riley, R. L. and Cournand, A. Analysis of factor affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs. I. Theory. *J. Appl. Physiol.*, 4: 77, 1951.
14. Riley, R. L., Donald, K. W. and Cournand, A.

Analysis of factors affecting the concentration of oxygen and carbon dioxide in the gas and blood of the lungs. II. Methods. *J. Appl. Physiol.*, 4: 102, 1951.

15. Van Slyke, D. D. and Sendroy, J., Jr. Studies of gas and electrolyte equilibria in blood. XV. Line charts for graphic calculations by the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. *J. Biol. Chem.*, 79: 781, 1928.
16. Austrian, R., McClement, J. H., Renzetti, A., Donald, K. W., Riley, R. L. and Cournand, A. Clinical and physiologic features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion. *Am. J. Med.*, 11: 667, 1951.
17. McClement, J. H., Renzetti, A., Carroll, D., Himmelstein, A. and Cournand, A. Cardiopulmonary function in hematogenous pulmonary tuberculosis in patients receiving streptomycin therapy. *Am. Rev. Tuberc.*, 64: 583, 1951.
18. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A. and Dresdale, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.*, 150: 315, 1947.
19. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D. and McGuire, J. Anoxia and human pulmonary vascular resistance. *J. Clin. Investigation*, 30: 957, 1951.
20. McClement, J. H., Renzetti, A., Himmelstein, A. and Cournand, A. Cardiopulmonary function in the pulmonary form of Boeck's sarcoid and its modification by cortisone therapy. *Am. Rev. Tuberc.*, 67: 154, 1953.

The Therapy of Sarcoidosis

FRANCIS J. LOVELOCK, M.D. *and* DANIEL J. STONE, M.D.
New York, New York

THE literature is replete with papers on the subject of sarcoidosis, reflecting a widespread and growing interest in this problem within recent years. Routine roentgenographic surveys of the chest within the past ten years have indicated that evidence of the sarcoid pattern can often be found in individuals who are free of symptoms or from whom minimal symptoms, at most, can be elicited after the existence of the disease is known. Many of these individuals would not have sought medical attention because of these mild symptoms.

Since symptoms are often minimal or absent, and clearing of pulmonary disease commonly occurs spontaneously, there is a widespread impression that sarcoidosis is a benign disease. Some studies,[1–3] however, have given special attention to the more serious aspects of this condition, including its chronicity, leading to varying degrees of irreversible pulmonary changes and the complication of tuberculosis. It has been emphasized by Reisner, for example, that over a five-year period of observation approximately one-third of patients with pulmonary sarcoidosis showed clearing of the roentgenographic abnormalities in the chest; the other two-thirds failed to clear or showed progression. The mortality rate in that series was 20 per cent and the majority of deaths were due to tuberculosis. Various other estimates of the frequency of tuberculosis as a complication of sarcoidosis range from 10 to 30 per cent.[4] There are numerous instances of severe fibrosis and emphysema resulting in death from cor pulmonale.[5–7] Our own experience with a group of cases of sarcoidosis has also led us to the opinion that this is not a benign disease.

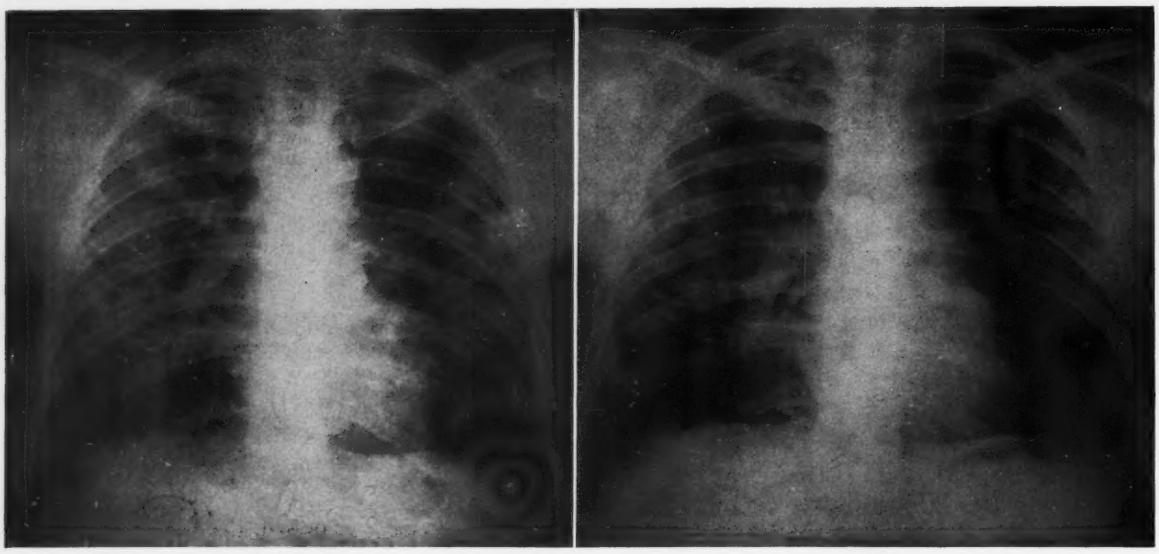
The purpose of this paper is to report on a group of thirty-nine proved cases of sarcoidosis showing involvement of the lungs and/or mediastinal and bronchopulmonary nodes. The duration of observation has ranged from several months to three and one-half years. Twenty-seven of these patients had received either no treatment at all or varying periods of bed rest, and have been observed on an ambulant status during most of this period. The remaining twelve patients received cortisone or ACTH therapy.

RESULTS IN PATIENTS NOT RECEIVING STEROID THERAPY

Two of these twenty-seven patients have been seen too recently for adequate evaluation. Follow-up of the other twenty-five indicates that eleven (44 per cent) have shown roentgenographic evidence of clearing of their pulmonary infiltration and diminution in size of the lymph nodes. In the majority this clearing was incomplete. Six (24 per cent) have either remained stationary or have shown varying degrees of progression roentgenographically; five (20 per cent) have developed tuberculosis. One patient (4 per cent) had a right middle lobectomy; there was no evidence of disease in the remainder of the lung. Two patients (8 per cent) have been lost to follow-up. Of the eleven patients who showed roentgenographic evidence of clearing, complete clearing with normal appearing films was noted in only three cases. Only one of these had had roentgenographic evidence of parenchymal disease at any time. The other two had nodal shadows only. Of the remaining eight patients seven had visible diffuse roentgenographic residues of varying extent, suggesting fibrosis and/or emphysema. One had localized residues only. Of the seven patients with diffuse involvement three had functional study and, as will be shown in another publication,[8] all three had definite abnormality of function, sometimes of a degree which could not be anticipated from the appearance of their roentgenograms.

RESULTS OF STEROID THERAPY

A previous communication[9] presented two cases of very rapid roentgenographic clearing of lesions diagnosed as pulmonary sarcoidosis. One was that of a patient with erythema nodosum with disseminated recurring pulmonary infil-



1A 1B

FIG. 1. A, immediately prior to therapy; B, after twelve days of cortisone.

tration, who had a positive Kveim reaction. Roentgenographic clearing was complete in this patient and has been maintained to date (seventeen months). In the other patient, a positive diagnosis of sarcoidosis was made by biopsy of a peripheral lymph node. Clearing was marked, although incomplete, in six days and persisted until the patient was lost to follow-up some two months later.

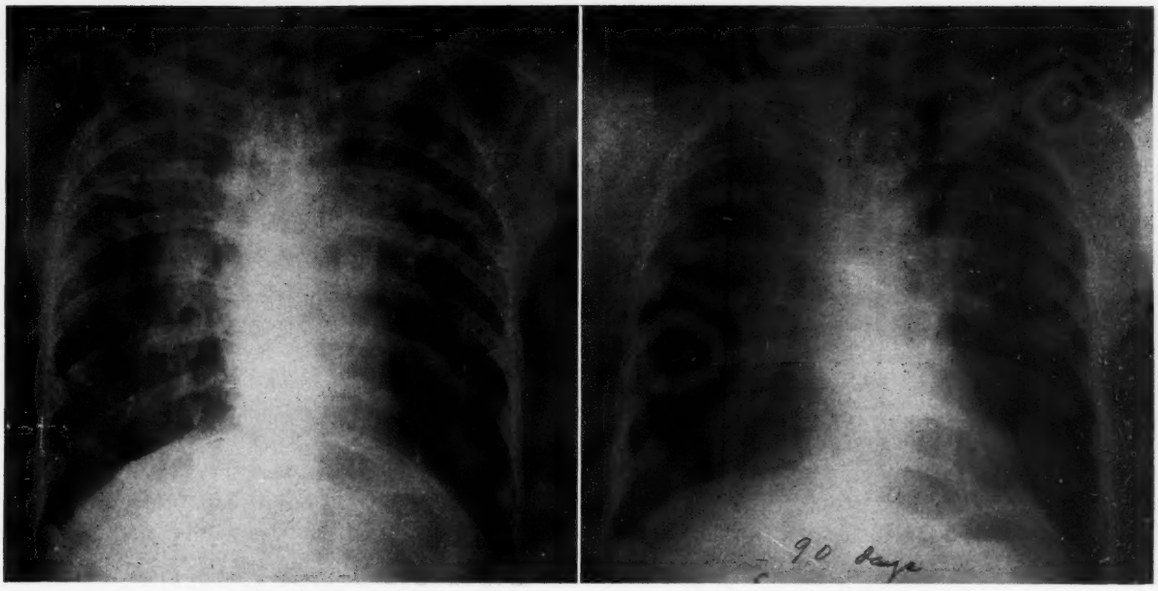
These initial rather spectacular results encouraged us to pursue the subject. To date we have treated a total of twelve cases, eleven of whom had pulmonary involvement with or without nodal involvement. Ten were treated with cortisone and one with ACTH. In one case it was learned that the patient had a positive gastric culture for M. tuberculosis immediately before therapy. This patient is therefore not included in the evaluation of roentgenographic response to cortisone. In the remaining ten patients follow-up has ranged from two months in one case to over one year in three cases, the remainder having been followed for six to nine months after completion of therapy.

The duration of therapy has varied from 30 to 135 days, the average being about 60 days. In the cortisone-treated patients the dose has been 300 mg. intramuscularly the first day, 200 mg. the second day and 100 mg. daily thereafter until the last few weeks of therapy, during which time it was gradually decreased. In the one patient treated with ACTH the dose was 25 mg. per day intravenously in one injection until the last two weeks, when it was gradually decreased. One patient had two courses of therapy totaling 135 days.

ILLUSTRATIVE CASE REPORTS

CASE 1. A twenty-five year old white male was admitted to Bronx V.A. Hospital July 17, 1951. There had been roentgenographic evidence of diffuse pulmonary infiltration since July, 1950. He had had a slight productive cough since 1948, dyspnea on exertion for one year and a weight loss of about 8 pounds in a year. There was no significant occupational exposure. The diagnosis of sarcoidosis was proved by biopsy of a subcutaneous nodule on the arm in the area of a tattoo and an axillary lymph node. The tuberculin test was negative through second strength PPD. The patient was observed at bed rest for almost a month. Cortisone therapy was begun on August 31, 1951 and discontinued on November 13, 1951. Roentgenographic evidence of clearing was prompt and marked. (Figs. 1A and B.) The patient also experienced very marked relief of exertional dyspnea.

One month after the completion of cortisone therapy, roentgenogram showed evidence of recurrence although the patient had maintained his subjective improvement. The tuberculin test was still negative. Cortisone therapy was resumed from March 11, 1952, and continued for sixty days. Again there was spontaneous and marked roentgenographic clearing, but again



2A 2B

FIG. 2. A, after a period of two months' bed rest. (Film identical with that taken on admission.) B, after three months of cortisone therapy.

within one month after discontinuance of therapy there was evidence of recurrence.

Comment. The reversibility of the roentgen shadows in such a short time suggests strongly, although it does not conclusively prove, that a considerable portion of the lesions are in an exudative rather than a granulomatous phase. Three additional patients exhibited this type of rapid response without subsequent exacerbation. That this encouraging evidence of clearing may sometimes be misleading is shown by functional studies on one of these patients, indicating the development of a diffuse fibrosis with impairment of diffusing capacity.[8]

CASE II. A twenty-five year old white male was admitted to Bronx V.A. Hospital January 25, 1951. There was a history of "pleurisy" in August, 1950. In October, 1950, he developed productive cough, mild dyspnea on exertion and malaise. There was a slight weight loss. The patient was thin and appeared chronically ill. There had been no unusual occupational exposure. There were scattered rales throughout both lungs. There were enlarged axillary lymph nodes. Roentgenograms showed diffuse pulmonary infiltration and enlargement of the mediastinal and bronchopulmonary nodes. (Fig. 2A.) Tuberculin test was negative through second strength PPD. A right thoracotomy was performed on April 27, 1951, and a biopsy of the right lung and mediastinal lymph nodes obtained. These showed a diffuse granulomatous process typical of sarcoid. Cortisone therapy was begun on June 11, 1951, and continued until September 12, 1951. There was marked relief of the patient's symptoms and roentgenograms showed evidence of gradual incomplete clearing. (Fig. 2B.) Total follow-up period is ten months and roentgenographic improvement has been maintained.

CASE III. A twenty-eight year old Puerto Rican male was admitted to the Bronx V.A. Hospital November 15, 1950. He had noted fatigability and some dyspnea on exertion for three months, associated with a mild pain in the right posterior chest which was not pleuritic in type. The patient did not appear ill, and the only abnormal findings were an enlarged right supraclavicular lymph node and several small, firm left axillary lymph nodes. Tuberculin test was negative through second strength PPD. Roentgenogram of the chest revealed diffuse parenchymal infiltration and enlarged mediastinal and bronchopulmonary nodes. Biopsy of a supraclavicular lymph node revealed a granuloma consistent with Boeck's sarcoid.

This patient was observed for almost four months on partial bed rest. During this period there was some indication of decrease in size of the lymph nodes but this change was minimal and the parenchymal infiltration did not substantially change. Cortisone therapy was begun

on March 21, 1951, and discontinued on May 1, 1951. Although there was a definite decrease in the patient's symptoms, roentgenographic change was slow and incomplete. Roentgenogram eight months after completion of treatment is substantially unchanged.

Comment. The type of response noted in Cases II and III suggests that some exudative and perhaps completely reversible disease was present in these patients but that granulomas and some fibrosis probably predominated at the time therapy was started. One of these patients, in spite of roentgenographic clearing, shows evidence of progressive functional deterioration.[8]

CASE IV. A thirty-seven year old white male was admitted to the Bronx V.A. Hospital November 11, 1950, with complaints of fatigue for five years and a productive cough, wheezing and exertional dyspnea for one year. Shadows were noted in a roentgenogram of the chest for the first time in May, 1950, and he was referred to another hospital with a provisional diagnosis of bronchial neoplasm. He refused exploratory thoracotomy and eventually was admitted to the Bronx V.A. Hospital.

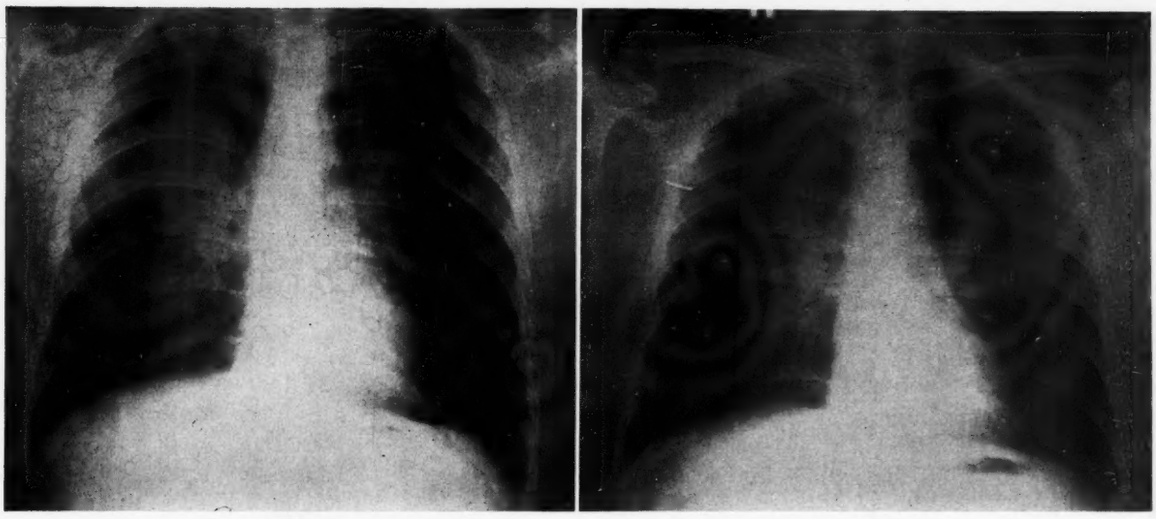
On examination he did not appear ill. The abnormal physical findings were limited to the chest where diminished resonance and breath sounds were noted on the right anteriorly and posteriorly, associated with intermittent wheezing heard throughout the chest but louder on the right side. Skin test with first strength PPD was strongly positive. Roentgenogram of the chest revealed infiltration extending from the right root toward the mid-lung field and the base. Bronchoscopy revealed some broadening of the carina and rigidity of the entire right bronchial tree. There was marked narrowing of the bronchus just below the orifice of the right middle lobe. The mucosa in this region was piled up, friable and bled easily. A biopsy was taken which showed a granulomatous lesion without caseation, typical of sarcoidosis. There was no evidence of neoplasm. Many smears and cultures of the sputum and bronchial aspirate were negative for M. tuberculosis. During the period of observation the reaction to tuberculin fluctuated in intensity, the patient sometimes reacting only to intermediate strength doses. Because of the apparently unilateral character of the lesion, the bronchial lesion, and the tuberculin reaction, it was believed that there was a good probability of tuberculosis in spite of the negative bacteriologic findings. A course of streptomycin and para-aminosalicylic acid was started on March 6, 1951. A second bronchoscopy on March 1, 1951, confirmed the gross findings of the first but another biopsy was not taken. Streptomycin and PAS were continued for six weeks, during which time there was no improvement in the roentgenographic appearance or in the patient's symptoms. Wheezing became more pronounced and the patient became more dyspneic. During this time a Kveim test started in February, 1951, became clinically positive and biopsy revealed a characteristic sarcoid pattern. Streptomycin was discontinued April 5, 1951. Cortisone therapy was begun May 14 and continued to July 11, 1951. The patient showed marked and prompt subjective improvement and disappearance of wheezing was noted early. Although wheezing recurred occasionally, this was minimal and was not associated with dyspnea. Unfortunately the patient did not permit further bronchoscopy. Roentgenographic change was not noted during the period of therapy or subsequently. (Figs. 3A and B.) On last examination July 24, 1952, the patient had maintained his subjective improvement for the most part. The physical examination revealed no evidence of wheeze. The roentgenogram showed no substantial change.

Comment. This patient had subjective and slight functional improvement without radiographic change. Although this case is somewhat complicated, it is believed that tuberculosis has been adequately ruled out and we believe that this is a case of sarcoidosis in which the parenchymal component has shown essentially no response to treatment. The interpretation of the changes in bronchial disease is difficult, particularly since bronchoscopic observation could not be made following therapy.

COMPLICATIONS IN PATIENTS TREATED WITH CORTISONE AND ACTH

Minor complications of therapy, such as fluid retention, acne, etc., occurred in a small percentage of cases but these were not considered significant. The major complications of therapy were the development of tuberculosis and functional deterioration. The latter will be discussed in a separate publication.[8]

Four patients of this group developed tuberculosis, all of them Negroes. Brief case reports are as follows:



3A 3B

FIG. 3. A, at start of cortisone therapy, following a period of bed rest and streptomycin. (This film was identical with that on admission.) B, after sixty days of cortisone therapy.

CASE V. A twenty-five year old Negro with disseminated pulmonary infiltration, moderate fever, severe dyspnea and cyanosis; a granulomatous lesion of the left choroid, with total loss of vision; a nodule in the left epididymis, and a peripheral lymph node interpreted histologically as sarcoid; negative tuberculin test, negative sputum and gastric cultures for M. tuberculosis over a period of six months. He was treated with streptomycin for ten days with no improvement. Cortisone was then added and subsidence of respiratory difficulty began almost immediately afterward. Cortisone and streptomycin were continued for two months, during which time there was marked improvement, the patient became afebrile for a time and the epididymal nodule shrank markedly. After sixty days of therapy, however, a tubercle bacillus highly resistant to streptomycin was obtained. He has had progressive pulmonary tuberculosis which has failed to respond to isoniazid.®

CASE VI. A thirty-one year old asymptomatic Negro male was admitted with tracheobronchial and bronchopulmonary adenopathy, a peripheral lymph node interpreted as sarcoid, diffuse pulmonary infiltration with evidence of bullous emphysema, negative tuberculin test and negative gastric cultures. After sixty days of cortisone therapy the tuberculin test became strongly positive and fever and weight loss developed. An infiltrate with a small cavity appeared in the right mid-lung field, and the sputum cultures became positive for M. tuberculosis, which was sensitive to streptomycin. In spite of absence of definite evidence of tuberculous foci other than in the lung and mediastinal nodes, this patient responded very poorly to streptomycin and para-aminosalicylic acid, the temperature remaining elevated for seven months. Although fever ultimately subsided and the temperature became normal, there has been only slight roentgenographic improvement.

CASE VII. A thirty-two year old Negro male was admitted with Marie-Strümpell arthritis, enlarged mediastinal nodes, minimal pulmonary infiltration and a nodule in the epididymis. The tuberculin test was negative; the Kveim reaction was positive. Gastric cultures were negative for M. tuberculosis. After thirty days of cortisone the tuberculin test became positive and three gastric cultures were positive for M. tuberculosis within two months. Roentgenogram showed no obvious change during that period. The patient signed out of the hospital and was lost to follow-up three months after completion of cortisone therapy.

CASE VIII. A thirty-seven year old Negro had had roentgenographic evidence of pulmonary infiltration for two years and recurrent sarcoid skin lesions during that time. He was negative to tuberculin, and many gastric cultures were negative for M. tuberculosis during a three-month period of observation. Cortisone therapy was started and slight roentgenographic clearing noted during the first week. Because of the appearance of edema and hypertension, however, therapy was discontinued after one month. It was then found that a gastric culture im-

mediately before therapy was positive for M. tuberculosis and repetition of the tuberculin test showed a positive reaction to intermediate strength PPD. This patient has had subsequent positive cultures for M. tuberculosis and is under treatment with streptomycin and para-amino-salicylic acid.

COMMENTS

When cortisone and ACTH became available and early studies indicated their capacity to retard the development of fibrosis in inflammatory conditions,[10] it was quite naturally supposed that these agents might have value in the therapy of sarcoidosis. This raises at once certain interesting questions regarding the pathology of this disease.

Sarcoidosis is characterized by the formation of granulomas,[7] the so-called non-caseating epithelioid tubercle, which tend to heal by fibrosis in the natural course of the disease. It is not known whether any type of therapeutic agent will cause the disappearance of these granulomas without leaving residues in the form of fibrosis. The findings on some biopsy material after cortisone therapy suggest that resorption of granuloma may occur.[11] More frequently, however, extensive granuloma is replaced by considerable fibrosis.

There is very little evidence to indicate precisely what type of pathologic change in tissue occurs prior to the development of a well established granuloma. Recent studies by Shay[12] of liver biopsies in sarcoidosis indicate that degenerative changes followed by infiltration of lymphocytes and histiocytes precede the development of the granuloma. Ricker et al.[7] noted that non-specific proliferation of sinusoidal reticuloendothelium occurred in the neighborhood of sarcoid granulomas, resulting in choking of the lymphatic sinusoids. They regarded this as a pregranulomatous lesion but were unable to demonstrate by serial section that the granulomas actually developed from the proliferated reticuloendothelium. It has been suggested to us by Amberson[13] that an exudative type of infiltration in the lung probably precedes the development of granuloma. It is quite possible, although we have no evidence for it, that this phase of pathologic involvement may persist for a long period. Biopsy of the lung of one of our patients did reveal a great variety of pathologic processes, ranging from simple edema through areas of exudative inflammation to fully developed sarcoid granulomas.

If such an exudative phase persists long enough, it seems quite possible that the use of cortisone and ACTH might aid in the resolution of this process without the development of appreciable fibrosis. If, on the other hand, granulomatous disease develops early, some resolution of granulomas might be hoped for but the degree of replacement by fibrosis may be considerable.

In this study of patients before and after cortisone and ACTH therapy it was hoped to obtain evidence to indicate resolution without significant fibrotic residuals. Four criteria were employed: (1) roentgenographic evidence of clearing, (2) pathologic studies of involved tissues after treatment, (3) evaluation of pulmonary function and (4) evidence of the development of tuberculosis.

Roentgenographic Evidence of Clearing. Various degrees of clearing were noted in a majority of patients so treated. If we exclude the three patients who developed tuberculosis after treatment, only one of the remaining seven treated with steroids failed to show clearing.

Pathologic Studies after Treatment. We have only a few studies comparable to those recently reported by Siltzbach[11] who found that ten of fourteen specimens obtained after treatment with ACTH or cortisone showed changes similar to those seen in the spontaneous healing of sarcoidosis lesions. In the majority the lesions were replaced by varying degrees of hyalinized connective tissue. Only one of these specimens, however, was obtained from the lung. In two of our cases we found similar hyalin fibrosis at the site of Kveim reactions. It is difficult from the observations available to estimate the extent of hyalin fibrosis which may occur in the lungs or to surmise from roentgenograms whether it is comparable in degree or exceeds that which occurs in the natural healing of these lesions. It seems possible that, in spite of roentgenographic evidence of clearing, healing with increased interstitial and peribronchial fibrosis might occur. This would be undesirable from the point of view of pulmonary function.

Evaluation of Pulmonary Function. Results of functional study in patients treated with cortisone and in the eleven patients not so treated are presented in a separate communication.[8] It will be obvious from these studies that one

can be seriously misled by the roentgenographic changes. Although functional improvement has been maintained in some patients, in others there has been functional deterioration in spite of roentgenographic improvement. Unfortunately, we know of no way to predict what type of change will occur with therapy.

Complication of Tuberculosis. It should be noted that in our twenty-five cases of sarcoidosis observed over a period of three and one-half years, without cortisone or ACTH therapy, tuberculosis developed in 20 per cent. The incidence in the cortisone-treated group is three patients out of eleven, or approximately 27 per cent. While the difference has no statistical significance the occurrence of these three complications in a short period of time, all in close association with cortisone therapy, indicates a definite hazard of treatment. It is significant that this complication occurred only in our Negro patients, in both the cortisone-treated and untreated groups, although the total cases of sarcoidosis are about evenly divided between whites and Negroes. This finding is confirmatory of reports in the literature.[2] Two of these three patients had palpable epididymal nodules before therapy suggesting prior tuberculous infection. These patients, however, were intensively studied bacteriologically and repeated tuberculin tests were negative. This led us to conclude that even though there may have been an antecedent tuberculous infection, it was inactive at the time and the clinical manifestations were due to sarcoidosis. Consequently, even if new progressive infection did not occur in association with cortisone therapy, there is good reason to believe that a previously inactive infection was activated.

SUMMARY AND CONCLUSIONS

1. The results of observations of a group of thirty-nine patients with pulmonary sarcoidosis are presented. The period of observation varied from several months to three and one-half years.

2. The natural evolution of this disease as observed in twenty-seven patients is compared with that following cortisone or ACTH therapy in twelve patients, principally in respect to roentgenographic changes in the lungs and complications of the disease.

3. A majority of patients with pulmonary sarcoidosis show some roentgenographic evidence of improvement following therapy with cortisone or ACTH but no criteria have been found which permit us to predict the extent of such improvement. A higher percentage of clearing was noted in patients receiving cortisone or ACTH (64 per cent) than in the untreated cases (44 per cent). Roentgenographic evidence of clearing is not always maintained, however, as indicated by one patient who had rapid recurrence after each of two courses of cortisone therapy.

4. The percentage of cases developing tuberculosis following therapy with cortisone and ACTH does not differ significantly from that found in the untreated cases. The rapid development of tuberculosis immediately following therapy in three patients, however, implies a serious hazard in this type of treatment. It appears significant that this complication was noted only in Negroes.

5. It is concluded that indications for the treatment of pulmonary sarcoidosis with cortisone or ACTH are not yet established.

REFERENCES

1. Reisner, D. Boeck's sarcoid and systemic sarcoidosis. *Am. Rev. Tuberc.*, 1: 49, 289, 1944; 2: 49, 437, 1944.
2. Riley, E. A. Boeck's sarcoid—a review based upon a clinical study of 52 cases. *Am. Rev. Tuberc.*, 62: 231, 1950.
3. Pinner, M. Non-caseating tuberculosis: analysis of literature. *Am. Rev. Tuberc.*, 37: 690, 1938.
4. Freiman, D. G. Sarcoidosis. *New Englnd J. Med.*, 1: 259, 664, 1948; 2: 259, 709, 1948; 3: 259, 743, 1948.
5. McCort, J. J., Wood, R. H., Hamilton, J. B. and Ehrlich, D. E. Sarcoidosis. *Arch. Int. Med.*, 80: 293, 1947.
6. Lovelock, F. J. and Stone, D. J. Unpublished observations.
7. Ricker, W. and Clark, M. Sarcoidosis: a clinical pathologic review of 300 cases, including 22 autopsies. *Am. J. Clin. Path.*, 19: 725, 1949.
8. Stone, D. J., Schwartz, A., Feltman, J. A. and Lovelock, F. J. Pulmonary function in sarcoidosis and results with cortisone therapy. *Am. J. Med.*, 15: 468, 1953.
9. Lovelock, F. J. and Stone, D. J. Cortisone therapy of Boeck's sarcoid. *J. A. M. A.*, 147: 930, 1951.
10. Ragan, C., Grokoest, A. W. and Boots, R. H. Effect of adrenocorticotrophic hormone (ACTH) on rheumatoid arthritis. *Am. J. Med.*, 7: 741, 1949.
11. Siltzbach, L. E. Effects of cortisone in sarcoidosis—a study of 13 patients. *Am. J. Med.*, 12: 139, 1952.
12. Shay, H., Berk, J. E., Sones, M., Aegerter, E. E., Weston, J. K. and Adams, A. B. The liver in sarcoidosis. *Gastroenterology*, 10: 441, 1951.
13. Amberson, J. B. Personal communication.

Renal Complications of Sarcoidosis and Their Relationship to Hypercalcemia*

With a Report of Two Cases Simulating Hyperparathyroidism

GERALD KLATSKIN, M.D. *and* MARTIN GORDON, M.D.

New Haven, Connecticut *Newington, Connecticut*

NEPHROLITHIASIS and nephrocalcinosis, and their sequelae pyelonephritis and azotemia, are well recognized complications of hyperparathyroidism[1,2] and a heterogenous group of disorders whose only common denominator is their association with hypercalcemia and/or hypercalcuria. Among the latter may be mentioned vitamin D intoxication,[3–5] osteolytic bone metastases[6] especially following estrogen and androgen therapy,[7] Paget's disease,[6] multiple myeloma,[8] osteoporosis of disuse,[9] renal tubular acidosis[6] and the prolonged excessive ingestion of milk and alkali.[10,11] Although the mechanisms underlying the disturbances of calcium metabolism in these conditions differ widely, their effects on the kidney are remarkably uniform, giving rise to characteristic pathologic changes and distinctive clinical features.

The occurrence of hypercalcemia in sarcoidosis was first recognized in 1939,[12] but its significance with respect to the development of renal complications in this disease was not appreciated for some time. However, in 1948 Albright and Reifenstein[6]† called attention to the fact that the hypercalcemia was associated with hypercalcuria and could produce nephrocalcinosis and renal stones. In a recent review of 160 cases of sarcoidosis seen at the Johns Hopkins and Massachusetts General Hospitals, Longcope and Freiman[14] found five instances of renal failure (two complicated by calculi), and two instances of renal calculi without renal insufficiency. These included the two cases previously reported by Albright and Reifenstein.[6] Hypercalcemia was present in all four cases with renal insufficiency in which the blood was examined, and in one of the two cases with uncomplicated stones. Of special interest was the demonstration of a relationship between the serum calcium level and renal function in one case, and the postmortem evidence of nephrocalcinosis, nephrolithiasis and pyelonephritis in another. While calcium deposits in the kidney had been noted previously in sarcoidosis,[15,16] this was the first case in which such deposits were correlated with an increase in serum calcium and in which their significance with respect to the pathogenesis of the renal failure was clearly defined. In several other previously reported *non-fatal* cases with azotemia[17–19] hypercalcemia was recognized but renal insufficiency was attributed to massive granulomatous invasion of the kidneys, an unlikely possibility in view of the rarity of extensive renal lesions in sarcoidosis.[14] Certainly the findings in Longcope and Freiman's case,[14] and the occurrence of generalized calcinosis[17] and calcific band keratitis[20]‡ in similar cases strongly suggest that when renal insufficiency supervenes in sarcoidosis it is usually due to nephrocalcinosis associated with hypercalcemia.

The renal findings and hypercalcemia in such cases may so dominate the clinical picture as to obscure the underlying disease and masquerade as hyperparathyroidism or primary kidney disease. Although the small numbers of previ-

† In a review on sarcoidosis written in the same year Freiman[13] came to the same conclusion on the basis of his observations on two cases seen at the Massachusetts General Hospital. Evidently these were the same cases described by Albright and Reifenstein.[6]

‡ Walsh and Howard[20] reported the occurrence of band keratitis in two cases of sarcoidosis. One of these was subsequently described by Longcope and Freiman[14] (Case 13) and was found to have azotemia and nephrolithiasis.

* From the Department of Internal Medicine of the Yale University School of Medicine, the Grace-New Haven Community Hospital, and the Veterans Administration Hospital, Newington, Conn.

ously reported cases would appear to speak for the rarity of this syndrome, there is reason to believe that it occurs more frequently than is recognized. The following case reports and review of the pertinent literature serve to illustrate these points.

CASE REPORTS

CASE I. J. B. (C43032), a sixty-eight year old white male, was first seen in the outpatient department of the Grace-New Haven Community Hospital on June 16, 1950, at which time he complained of weakness of three years' duration. He was admitted to the hospital on July 10, 1950.

In September, 1947, the patient had noted the onset of fatigue and anorexia, followed by a weight loss of 35 pounds over a period of two months. His only other complaints were an early morning cough productive of small amounts of sputum and slight dyspnea on exertion which had been present for several years. He had never noted orthopnea, edema or angina.

He first sought medical attention in November, 1947, at which time he was told that he had "a lung condition." In January, 1948, and again in March, 1948, he was hospitalized for short periods. No definite diagnosis was established but the patient was advised to take a high-protein, high-caloric diet. This resulted in an increase in weight but did not alleviate his weakness.

A year later, in May, 1949, the patient was admitted to the Mount Zion Hospital in San Francisco* for the same complaints. On the basis of the x-ray findings in his chest a diagnosis of pulmonary fibrosis was made. Ten months later (March, 1950) he was re-admitted to the same hospital because of urinary frequency and an enlargement of the right index finger which had been present for six weeks. Physical examination revealed firm, non-tender masses in the soft tissues of the left thumb and right index fingers which, on x-ray examination, proved to be calcified. In addition, similar calcified deposits were discovered in the soft tissues about the left shoulder. X-ray examination of the bones failed to reveal any abnormalities. The chest x-ray once again showed extensive pulmonary fibrosis. The serum calcium level was found to be elevated, 11.5, 11.5, 13.0 and 15.0 mg. per 100 ml., on four occasions, and there was evidence of hypercalcuria. On a low-calcium diet (content not stated) for a period of six days, the patient excreted 500 mg. of calcium per day in his urine. The alkaline phosphatase level was within normal limits on three occasions. Total serum protein concentration ranged between 6.5 and 7.5 gm. per 100 ml. (albumin and globulin fractions not reported). Tests for Bence-Jones protein in the urine were uniformly negative. Other details of the urinalyses carried out at this time are not known. However, there was definite evidence of azotemia, the non-protein nitrogen in the serum ranging between 66 and 90 mg. per 100 ml., and phenolsulphonphthalein excretion being reduced to 5 per cent in two hours.

Because of the hypercalcemia and metastatic calcification a diagnosis of hyperparathyroidism was entertained. Accordingly an exploration of the neck was carried out on March 20, 1950. The parathyroid glands, which were all identified, appeared to be normal in size and one removed for microscopic study revealed normal histologic features. An enlarged left axillary node, which had been noted prior to his operation, was removed for biopsy. This revealed multiple focal granulomas suggestive of Boeck's sarcoid.

Following his operation the patient was kept on a low-calcium intake for a short time without any apparent effect on the hypercalcemia or hypercalcuria. When he was discharged from the hospital at the end of March, the serum calcium was still elevated (11.5 mg. per 100 ml.), and the Sulkowitch test[21] on his urine was strongly positive but the patient felt somewhat better and he returned to his home.

Except for hyperthyroidism, relieved by subtotal thyroidectomy at the age of fifty-two (1934), and an attack of gonorrheal urethritis and epididymitis at the age of twenty, the patient had had no other significant illnesses. There were no symptoms of thyroid disease following his operation and a recent basal metabolic rate had been within normal limits.

There was no history of exposure to beryllium, silica dust or tuberculosis, and the patient had never had skin lesions, iritis, choroiditis or parotitis. As far as he was aware he had had no fever. The urinary frequency which he had experienced in March, 1950, was no longer present but the urinary stream was somewhat

* The authors are indebted to Dr. Robert Kalmansohn for a clinical abstract of the patient's findings at the Mount Zion Hospital.

weak, as it had been for some time. At no time had he experienced renal colic or hematuria.

The family history was non-contributory.

When first seen at the Grace-New Haven Community Hospital on June 16, 1950, he had gained 20 pounds in weight and had a good appetite. However, he was still 12 pounds under his usual weight of 135 and felt weak and dyspneic. In addition he had been troubled for two months with pain and stiffness in the left shoulder and elbow, and in both knees and thighs. These were aggravated by muscular activity following periods of immobilization and were relieved by analgesics. His cough had not changed appreciably but there had been slight blood-streaking of the sputum for two weeks.

Physical examination revealed a slender, white-haired old man who did not appear ill. Despite the history of weight loss there was no evidence of malnutrition. The temperature, pulse rate and respirations were normal, and there was no dyspnea, cyanosis or clubbing. The blood pressure was 130/80 mm. Hg and remained within normal limits on several subsequent determinations. On the volar surface of the left thumb could be felt a minute, firm, subcutaneous nodule. No other significant skin or subcutaneous lesions were noted. The pupils, extra-ocular movements and fundi were normal except for a mild degree of retinal arteriosclerosis. No lesions were noted in any of the mucous membranes. The parotid and lacrimal glands were not enlarged or indurated. A thyroidectomy scar was present in the lower neck; no glandular tissue or masses could be felt. A small mass of soft, discrete lymph nodes was palpable in the right axilla. The anteroposterior diameter of the chest was increased and the breath sounds were distant but expansion and resonance were normal and no rales were audible. The heart was of normal size; the sounds were of good quality, the rate and rhythm were normal and there were no murmurs. The peripheral arteries were slightly thickened and the dorsalis pedis pulsations were absent. A soft, thin, smooth, non-tender liver edge could be felt two fingerbreadths below the costal margin but neither the spleen nor the kidneys were palpable. The external genitalia were normal except for slight atrophy of the left testis. The prostate was symmetrically enlarged, firm and smooth. The joints and bones showed no gross abnormalities.

Hematologic examination showed red cell count 3.6 million per cu. mm.; hemoglobin 13 gm. per 100 ml.; white cell count 8,950 per cu. mm.; differential count: polymorphonuclear cells 78 per cent, lymphocytes 18 per cent, monocytes 4 per cent; hematocrit 30 per cent; sedimentation rate 49 mm. in one hour (corrected rate 32 mm.). The urine had a specific gravity of 1.015, showed a trace to 1+ protein, and contained no formed elements. The Sulkowitch test on two occasions did not indicate excessive hypercalcuria. Phenolsulphonphthalein excretion was less than 10 per cent in two hours. The serum non-protein nitrogen was 70 mg. per 100 ml.; total proteins 7.2 gm. per 100 ml. (3.8 albumin, 3.4 globulin) and again 7.0 gm. per 100 ml. (3.6 albumin, 3.4 globulin); serum calcium 11.6 and later 12.9 mg. per 100 ml.; inorganic phosphorus 4.9 and 5.2 mg. per 100 ml.

Liver function tests revealed the following: Serum bilirubin 0.09 mg. per 100 ml. direct, and 0.72 mg. per 100 ml. total; bromsulphthalein test (5 mg. per kg.) 5.5 per cent retention in forty-five minutes; cephalin-cholesterol flocculation 1+ in twenty-four hours and 2+ in forty-eight hours; thymol turbidity 7.7 units; thymol flocculation negative; serum alkaline phosphatase 5.3 Bodansky units (within normal limits by the Shinowara, Jones and Reinhart method[22]); urine bile negative; urine urobilinogen 0.72 Ehrlich units in two hours; prothrombin time 100 per cent of normal.

The Mazzini test and Brucella agglutinations were negative. Skin tests with tuberculin, histoplasmin and brucellergen were also negative. Gastric washings were negative for acid-fast bacilli.

A liver biopsy (Vim-Silverman needle) revealed several granulomas composed of compact masses of epithelioid cells and occasional giant cells containing a few vacuoles and inclusion bodies; other lesions showed varying degrees of fibrosis; acid-fast stains failed to reveal any organisms. The lesions were regarded as compatible with the diagnosis of Boeck's sarcoid. (Fig. 1.)

X-ray studies showed diffuse fibrosis throughout both lungs, most marked at the apices. There was considerable osteoporosis of the spine and pelvis with compression fractures of the first and second lumbar, and the seventh dorsal vertebral bodies; the bones of the hands and feet appeared normal, but there was considerable periarticular and soft tissue calcification of the fifth left toe and right index finger, a small

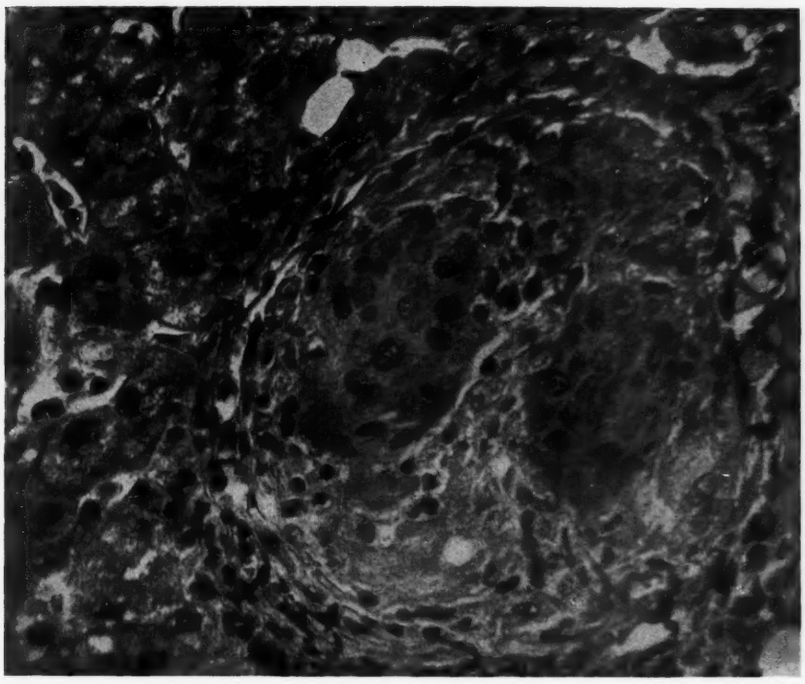


FIG. 1. Liver biopsy in Case 1; × 200. A fairly early granuloma, composed of a compact mass of epithelioid cells and two large giant cells surrounded by a delicate connective tissue capsule, is illustrated. Other sections showed older, densely fibrotic lesions.

amount of calcium in the soft tissues of the left thumb, and marked calcification of the digital vessels of the feet.

The kidneys were of normal size and there was no evidence of renal calculi or calcification; the distal aorta and its branches were markedly calcified.

Comment. The sequence of events in this case suggests that sarcoidosis, predominantly pulmonary in distribution, had been present for some time. In association with a recrudescence of the disease three years prior to his most recent hospital admission the patient had developed hypercalcemia and hypercalcuria, azotemia presumably on the basis of nephrocalcinosis, and metastatic calcification of the subcutaneous tissues and many of the arteries. Despite the absence of hypophosphatemia, which was attributed to the concurrent renal failure, and the absence of classical bone lesions, which is not unusual, the findings were considered sufficiently suggestive of hyperparathyroidism to warrant surgical exploration of the neck. This revealed normal parathyroid glands. Although hyperparathyroidism and other causes for hypercalcemia appeared to have been excluded, the significance of the granulomatous lesions demonstrated in the axillary lymph node, in relation to the pathogenesis of the renal failure, was not appreciated for some time.

The demineralization of the spine and pelvis, of sufficient severity to produce compression fractures of the vertebrae, is of particular interest in this case, both with respect to its pathogenesis and to its possible relationship to the hypercalcemia. Certainly these are not the usual bone changes seen in sarcoidosis so that the question of senile or some other type of osteoporosis, or of hyperparathyroidism secondary to renal disease may be raised. However, hypercalcemia is rare in senile osteoporosis[6] and there is no evidence to suggest that any of the other causes for osteoporosis was present. As for secondary hyperparathyroidism, it would appear to have been adequately excluded by the surgical findings and by the histologic features of the parathyroid gland removed at operation. The conclusion finally reached, that the bone decalcification was the result of sarcoidosis, is supported by the evidence presented by Schaumann[23] that diffuse invasion of the bone by granulomatous lesions may give rise to the picture of osteoporosis roentgenologically, and by previous reports of vertebral involvement[24] and decalcification of the long bones in sarcoidosis.[18]

The renal picture presented by this patient

was characterized by transient polyuria, persistent azotemia, hyposthenuria, minimal albuminuria without cylindruria or hematuria, and the absence of hypertension and retinopathy, a syndrome identical with that described in hyperparathyroidism,[2] vitamin D intoxication[5] and a variety of other conditions leading to nephrocalcinosis. Unfortunately it was not possible to follow the course of the renal disease in this case, particularly to observe the effects of a spontaneous or therapeutically induced regression of the granulomatous process.

Case II. K. B. (No. R58,343), a fifty-one year old white male, was admitted to the Newington Veterans Administration Hospital on June 11, 1951, complaining of abdominal pain, tarry stools, anorexia and an 18 pound weight loss of nine months' duration.

In September, 1950, nine months before admission to the hospital, the patient had noted the onset of post-prandial, crampy, left mid-abdominal pain, associated with eructations of sour, foul-smelling gas, and the passage of considerable flatus and frequent, loose, tarry stools. These recurred after each meal, were aggravated by fried foods, cabbage and cucumbers, and were relieved to some extent by the ingestion of alkalies and the passage of stools. At the same time unusual dryness of the mouth and anorexia were noted, and the patient began to lose weight.

The following month oatmeal was added to each of his meals and this appeared to reduce the frequency of both the abdominal pain and the diarrhea, and the stools returned to their normal color. However, there were exacerbations in February and March, 1951, which were associated with tarry stools once again. Since then the pain had been intermittent and the stools had remained normal in color. There was no history of previous indigestion, food intolerance, nausea, vomiting, hematemesis or disturbance of the bowels.

The gastrointestinal complaints were at no time accompanied by urinary symptoms. However, for several months the patient had noted nocturia (× 5) which he attributed to an increase in his water consumption related to the unusual dryness of his mouth, and two months after the onset of his present illness (November, 1950) he had experienced severe left-sided renal colic and passed a pea-sized, white stone. Except for the persistence of nocturia there were no further urinary symptoms until a few weeks before admission when some gravel was passed.

The patient had had an attack of "rheumatism" of the knees at the age of ten, and an appendectomy performed for acute appendicitis at the age of thirty-two. During the preceding six years he had suffered typical attacks of angina pectoris relieved by sublingual nitroglycerine. There was moderate dyspnea on exertion but no orthopnea or edema. There was no history of previous hypertension. The patient could not recall any skin or ocular lesions, lymphadenopathy, parotitis or pulmonary symptoms. The family history was non-contributory.

Physical examination disclosed the patient to be well developed and well nourished, and he did not appear ill. The temperature was normal, the pulse rate increased slightly to 100 and the blood pressure 170/90 mm. Hg. No skin or bone lesions, lymphadenopathy or enlargement of the parotids or lacrimal glands were noted. The fundi were normal in all respects. The thyroid was not enlarged and no cervical lymph nodes could be felt. Cardiac outline was normal by percussion, the sounds were of good quality and the rhythm was normal. Over the mitral area a soft, grade 1 systolic murmur was audible but it was not transmitted and was not accompanied by a thrill. No abnormalities of the peripheral arteries were noted. There was voluntary spasm of the abdominal wall but no significant tenderness. The edge of the liver could be felt one fingerbreadth below the costal margin, but was not regarded as enlarged since the upper limit of hepatic dullness was in the sixth interspace. Neither kidney was palpable, and there was no costovertebral angle tenderness. No other intra-abdominal masses were felt, although one observer reported a palpable spleen at the left costal margin. The genitalia were normal. No peripheral edema or clubbing was present.

Laboratory data were as follows: Hemoglobin 15 gm. per 100 ml.; white blood cells 5,600 per cu. mm.; differential count: polymorphonuclear cells 57 per cent, lymphocytes 38 per cent, monocytes 3 per cent and eosinophils 2 per cent. Urine analyses and blood chemistry are shown in Table I. Three random specimens of feces demonstrated no occult blood. The Mazzini test was negative. Urine cultures on several occasions were negative for bacteria. One urine and three sputum and gastric-washing concentrates were negative for tubercle bacilli on guinea-pig inoculation. The tuberculin test with 1st strength PPD was negative; with 2nd strength PPD it was positive.

TABLE I

SUMMARY OF URINE AND BLOOD ANALYSES IN CASE II

	Urine							PSP		Serum							
Date	Specific Gravity	Albumin	R.B.C. (/hpf)	W.B.C. (/hpf)	Hyal. Casts (/lpf)	Gran. Casts (/lpf)	Sulkowitch	15 Min. (%)	Total 1 hr. (%)	NPN (mg. %)	Total Protein (gm. %)	Albumin (gm. %)	Globulin (gm. %)	Ca (mg. %)	P (mg. %)	Alkaline Phosphatase (Bodansky units)	
6/11/51	1.007	Trace	0	10–12	occ.	occ.											
6/12/51	1.004	0	0	1–2	0	0		15	30								
6/13/51	1.010	Trace	0	10–15	0	0				72							Calcium oxalate crystals in urine
6/14/51										114							
6/15/51										74					3.7	5.7	
6/18/51	1.012	0	0	Many	0	0	Upper normal			66							Bence-Jones neg.
6/19/51																	Concentration test max. sp. gr. 1.007
6/20/51														12.8			3 glass test: tr. alb. many w.b.c. in all specs.
6/21/51											7.5	4.0	3.5				
6/22/51										69							Bence-Jones neg.
6/25/51														12.5	4.2		Urine culture neg.
7/2/51										56							
7/5/51											7.7	4.1	3.6				
7/6/51															3.1	6.7	Urine culture neg.
7/9/51										54							
7/13/51														12.1			
7/16/51										48							
7/23/51	1.006	Trace	0	Many	0	0				51					3.4		Acid phosphatase 0.3 B.u.
7/24/51											7.0	4.0	3.0				
7/26/51	1.005	0	0	0	0	0											Urine culture neg.
7/27/51																	Urine guinea pig neg.
Forced Fluids and Low Calcium, Acid-Ash Diet																	
3/17/52	1.018	1+	10	2–3	0	0		7	18								
3/19/52	1.028	1+	1–2	5–7	0	0		14	36	52				10.7	2.8		Urine culture neg.
3/26/52							normal								2.6	6.8	Acid phosphatase 0.4 B.u.
4/7/52	1.020	0	0	4–6													Oxalate crystals in urine
4/18/52										40				10.7	2.3	6.1	
4/22/52														9.9			Parathyroid exploration
4/30/52	1.017	0	0	1–2	0	0								10.3			
6/4/52										39				10.0	2.9		
6/11/52																	Concentration test max. sp. gr. 1.022

Liver function tests revealed total serum bilirubin 1.1 mg. per 100 ml.; cephalin-cholesterol flocculation 2+ in twenty-four hours; thymol turbidity 0.5 units; bromsulphthalein test (5 mg. per kg.) 1 per cent retention at forty-five minutes.

A gastric analysis was performed and showed the fasting specimen to contain 27 units of free hydrochloric acid.

An electrocardiogram revealed changes compatible with an old anterior septal myocardial infarction. X-ray studies of the chest demonstrated bilateral hilar adenopathy with pulmonary congestion and diffuse fine nodularity throughout both lung fields; the cardiac silhouette was normal. No abnormalities were demonstrable in the skull, pelvis, spine or hands on bone x-rays. Those of the abdomen revealed calcified densities in the region of the kidney shadows bilaterally. Retrograde pyelograms revealed bilateral renal calculi. No abnormalities of the esophagus, stomach, small intestine or colon were demonstrated.

Cystoscopy revealed cystitis follicularis in the region of the bladder neck; PSP appearance time four minutes on the right, six minutes on the left; PSP excretion in fifteen minutes: 7.5 per cent on the right and 7.5 per cent on the left; a urine specimen from the right ureter revealed granular casts and epithelial cells, that from the left ureter occasional white blood and epithelial cells.

The effects of an intravenous injection of 300 units of parathyroid extract on the urinary excretion of inorganic phosphorus were as follows:

Time (hr.)	Urine P Concentration (mg. per 100 ml.)	P Excreted (mg. per hr.)
1 (control)	36.5	37.6
2 (control)	35.5	38.0
Parathyroid extract (300 units)		
3	40.0	42.0
4	54.0	37.8
5	57.0	33.0

The very slight increase in phosphate excretion following a large dose of parathyroid extract was regarded as subnormal and was attributed to the associated renal failure. Normally a twofold or greater increase in phosphate excretion is seen with even smaller doses of parathyroid extract.[25]

Liver biopsy (Vim-Silverman needle) specimens obtained on two separate occasions revealed the presence of periportal granulomas composed of compact masses of epithelioid cells and occasional giant cells, without significant leukocytic infiltration or necrosis; many of the lesions were densely fibrotic; acid-fast stains failed to reveal tubercle bacilli; the lesions were considered compatible with the diagnosis of sarcoidosis. (Fig. 2.)

Bone marrow aspiration (sternum) failed to reveal the presence of granulomas.

During the course of these investigations the patient was entirely symptom-free. However, the non-protein nitrogen, which was elevated to 52 mg. per 100 ml. on admission, rose to a peak of 114 mg. in a few days but fell slowly to a level of 51 mg. per 100 ml. following an increase in fluid intake. The urine concentration remained low at all times, even when fluids were restricted for a period of fifteen hours. The blood pressure was labile, varying between 100/70 and 170/110 mm. Hg; however, it was within normal range more often than not. The serum calcium level, which was significantly elevated on admission (12.8 mg. per 100 ml.), did not change significantly, and the serum inorganic phosphorus remained within normal limits. At no time was the patient febrile.

Since it was now the consensus that the hypercalcemia and azotemia were probably related to sarcoidosis rather than to hyperparathyroidism, an attempt was made to study the effects of a low-calcium, acid-ash diet and forced fluids, since these appeared to have been partially effective in Case 1. Accordingly treatment was begun on July 30th, and the patient was discharged to the care of his physician on August 10, 1951, with instructions to continue this regimen at home.

During the next six months the patient felt exceedingly well and gained 18 pounds in weight. However, early in February, 1952, he developed typical left renal colic and gross hematuria, and shortly thereafter passed a large multifaceted calculus. It was decided to admit the patient to the hospital on February 17, 1952, for re-evaluation.

At this time the physical examination failed to reveal any abnormalities. The blood pressure was 160/80 mm. Hg. Once again the urine

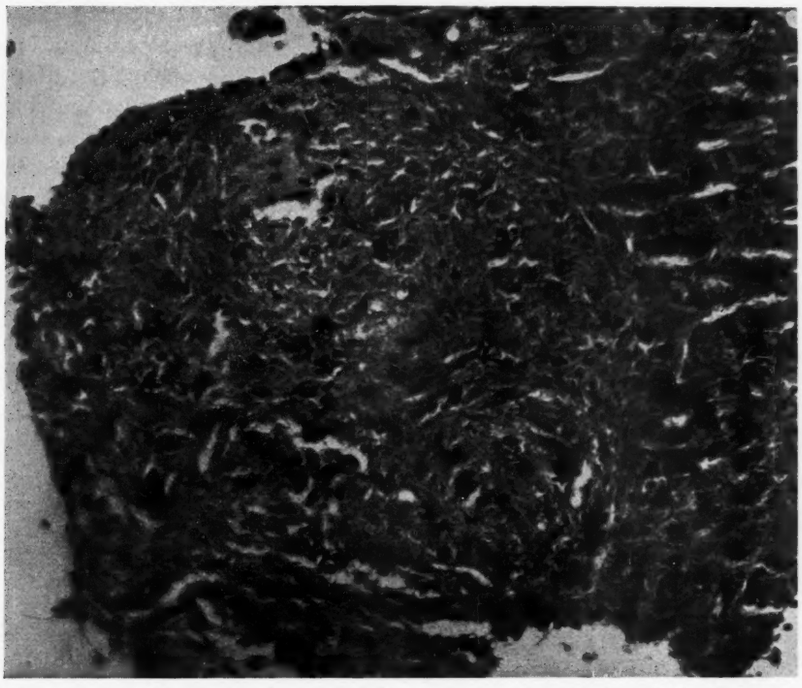


FIG. 2. Liver biopsy in Case II; × 200. An old, densely fibrotic lesion, containing the remnants of a giant cell, is illustrated. Other sections showed younger lesions with many epithelioid cells but all were fibrotic to a greater or lesser extent.

showed a small amount of albumin but now the specific gravity was up to 1.018, and on subsequent examinations it ranged from 1.016 to 1.028. In addition, a few red blood cells were demonstrated microscopically, and the Sulkowitch test once again showed a normal urine calcium concentration. Phenolsulphonphthalein excretion had not changed significantly: 13 per cent in fifteen minutes and a total of 37 per cent in one hour (previously it had been 15 and 30 per cent, respectively). The non-protein nitrogen was again elevated to a level of 52 mg. per 100 ml. of plasma but all subsequent determinations were within normal limits. The serum calcium had decreased appreciably, and was now within the normal range, 10.7 mg. per 100 ml. An unexpected finding was a slight but significant lowering of the serum inorganic phosphorus to 2.8 mg. per 100 ml., a borderline subnormal value in this laboratory. The serum alkaline phosphatase was still slightly elevated to 6.8 Bodansky units (normal values by Bodansky method employed under 5 units). Repeat x-ray examinations revealed some regression of the hilar adenopathy previously noted in the chest, the presence of calcified stones in the pelvis and ureter of the left kidney and a well defined lamina dura about the teeth.

At this time the patient was under the care of a new group of physicians who believed that, despite the unequivocal evidence of sarcoidosis on the one hand and the absence of generalized decalcification and the presence of a normal lamina dura on the other, hyperparathyroidism had not been adequately excluded. For that reason surgical exploration of the neck was recommended. At operation, which was carried out on April 21, 1952, the thyroid gland was found to be of normal size and consistency, except for a poorly circumscribed, firm nodule which projected from the posterior aspect of the mid-portion of the right lobe. This was excised for histologic study. On the right side two slightly brownish nodules were identified as parathyroids. The more superior was 4 mm. in diameter, while the inferior, which was lateral and posterior to it, measured 8 mm. in diameter. The latter was presumed to be a parathyroid adenoma and was therefore removed. On the left side a 4 mm. inferior parathyroid gland was identified but the superior gland could not be found. Exploration of the space of Burns and the posterior-superior mediastinum failed to disclose any aberrant parathyroid tissue. Histologic sections of the nodule revealed a granulomatous structure surrounded by normal thyroid

tissue, which was considered compatible with a diagnosis of sarcoidosis of the thyroid gland. The second specimen, removed from the thyroid gland itself, was composed of normal thyroid tissue.

Postoperatively the patient made an uneventful recovery. On June 6, 1952, the non-protein nitrogen was 39 mg., the serum calcium 10.0 mg. and the serum inorganic phosphorus 2.9 mg. per 100 ml., essentially as before operation. However, the concentration of the urine during a Mosenthal test now rose to a maximum specific gravity of 1.022, a distinct improvement over previous tests. The average daily fluid intake remained approximately 3,500 ml., while the average urinary excretion was 2,200 ml. The blood pressure ranged between 110/70 and 140/80 mm. Hg.

The patient was discharged from the hospital on June 12, 1952, and was advised to continue on his low-calcium, acid-ash diet and to return for periodic re-examination.

Comment. The history of nocturia, renal calculi and unusual thirst in this case at once suggested the possibility of hypercalcemia and this was soon confirmed. However, the nature of the disturbance in calcium metabolism remained in doubt for some time. Initially hyperparathyroidism appeared to be the most likely possibility, although the absence of hypercalcuria and hypophosphatemia, and the persistence of an intact lamina dura about the teeth were strong points against the diagnosis. Sarcoidosis was not considered at all, since there were no overt signs to suggest it. However, directly the initial roentgenogram of the chest revealed hilar adenopathy the similarity of the findings to those in Case 1 was recognized, and sarcoidosis was suggested as the probable cause of both the hilar adenopathy and the hypercalcemia, which by now was known to be associated not only with nephrolithiasis but also with a significant degree of renal insufficiency. This opinion appeared to be confirmed by the histologic demonstration of sarcoidal lesions in the liver; however, several experienced observers took the point of view that, while this evidence substantiated the diagnosis of generalized sarcoidosis, it did not necessarily exclude the presence of co-existent hyperparathyroidism. For that reason surgical exploration was carried out, but no parathyroid adenoma was found.

In contrast to Case 1, there was no evidence of decalcification; nor could hypercalcuria be demonstrated by the Sulkowitch test, despite the presence of hypercalcemia and multiple calcified renal stones. However, the first test was carried out at a time when the urine was low in concentration and high in volume, so that the factor of dilution may have played a role in producing a normal result, while the second test was not performed until the serum calcium had returned to a normal level. Unfortunately a proper calcium balance study was not carried out so that hypercalcuria was by no means excluded with certainty.

The importance of needle biopsy of the liver in the diagnosis of sarcoidosis is well illustrated in this case. As pointed out previously,[26] histologic confirmation is essential so that in the absence of more readily accessible lesions liver biopsy may be the only means of establishing the diagnosis. In the present case the only evidence of sarcoidosis was the x-ray finding of hilar adenopathy and pulmonary infiltration, but even these were equivocal initially. An experienced radiologist who examined the first set of films without knowledge of the complete clinical history interpreted these findings as compatible with perihilar and pulmonary congestion and edema related to uremia. It was the association of these findings with hypercalcemia and azotemia, and their resemblance to those in Case 1, that called the attention of the clinicians to the possibility of sarcoidosis. Unfortunately, the usual confirmatory findings sought in that disease, a negative tuberculin test, hyperglobulinemia, characteristic bone cysts and the presence of lesions in the other known sites of predilection were completely lacking. However, despite the absence of clinical signs of hepatic involvement the liver revealed typical granulomatous lesions compatible with sarcoidosis.

DISCUSSION

The kidneys are not infrequently the site of granulomatous infiltration in sarcoidosis. Indeed, in some autopsy series[14,27] the incidence has been as high as 20 per cent. However, the lesions are usually so small and few in number that they rarely produce significant impairment of renal function.[14] Extensive infiltration of the kidneys, on the other hand, occasionally leads to renal insufficiency, as in Chanials' case,[28] but may not in all instances.[29,30]

At least seventeen other instances of renal failure have been reported in sarcoidosis, in-

cluding three in which the postmortem findings are known (Table II, foot-note). Renal granulomas were demonstrated in all three autopsied cases but in none did they appear to be the major factor in producing renal insufficiency. In one of Ricker and Clarke's cases[27] renal failure was due to arteritis and periarteritis of the renal vessels. In another, reported by Longcope and Freiman,[14] it was ascribed to pyelonephritis secondary to nephrolithiasis and nephrocalcinosis. In the case described by Horton, Lincoln and Pinner[15] the kidneys were contracted, and showed calcification and marked degeneration of the tubules, hyalinization of the glomeruli and an interstitial inflammatory reaction; findings compatible with, although not necessarily diagnostic of, hypercalcemic nephrocalcinosis.[31] Unfortunately the serum calcium was not determined in the latter case.

The evidence is strongly suggestive that renal failure was due to nephrocalcinosis in at least nine of the fourteen *non-fatal* cases. (Table II.) Thus all nine exhibited hypercalcemia and clinical features consistent with nephrocalcinosis, six had hypercalcuria, four had renal calculi, one had metastatic calcification of the kidneys and two had calcification of the other tissues. In the remaining five cases (Table II, foot-note) the renal symptoms and urinary findings were suggestive of nephrocalcinosis but the serum calcium was not determined in four (Cases XI, XIII, XIV and XVI) and was normal in one (Case XV) on a single occasion, so that the nature of the renal lesion in these cases remains in doubt.

No better description of the clinical features of nephrocalcinosis can be given than the following abstract from an early paper on the renal complications of hyperparathyroidism by Elsom and his associates:[2] ". . . certain common features are worthy of mention in considering whether any basis exists for differentiation of this from other types of chronic renal disease. Many of the usual concomitants of chronic nephritis, e.g., retinal exudates and hemorrhages, cardiac enlargement and peripheral edema, are absent or very inconspicuous. . . . A marked grade of renal insufficiency may exist, as in the present patient, without elevation of the blood pressure. The urinary sediment is unusual in that the excretion of red cells, casts and albumin seem low in proportion to the degree of functional failure present. No one of these unusual features constitutes a trustworthy differential point, but together they result in a clinical picture sufficiently bizarre to suggest a search for other causes of renal failure. . . . Polyuria, nocturia and polydipsia occur with striking frequency . . . and may be due to renal damage with consequent inability to excrete urine of high specific gravity. However, the fact that these symptoms frequently disappear immediately after removal of a parathyroid tumor suggests that they do not necessarily indicate structural renal damage, but are rather the consequence of the excessive urinary excretion of calcium and phosphorus. When the inability to elaborate concentrated urine persists . . . for many months after correction of the disturbed mineral metabolism, it must be attributed to more permanent structural damage."

Clinical descriptions of nephrocalcinosis due to other causes[2,5] conform closely to this pattern and, as is evident from the summary in Table II, the same may be said of the renal failure associated with hypercalcemic sarcoidosis. It will be noted that in the group of seven cases in which adequate data were available for analysis only one had a sustained hypertension (Case III). With two exceptions (Cases IV and VI), none had cardiac enlargement, edema or retinopathy. Azotemia, hyposthenuria and polyuria occurred with striking regularity while albuminuria, cylindruria and hematuria were either absent or inconspicuous. The polyuria in Case I may well have been due to excessive excretion of calcium and phosphate since it subsided when the urine calcium concentration fell despite the persistence of azotemia, but in the other cases the sustained polyuria almost certainly indicated structural changes in the kidney.

Especially noteworthy was the relatively benign course of the disease in this group. Considering the severity and duration of their renal insufficiency (Table II) and the wide dissemination of their sarcoidal lesions, it is surprising that only one death occurred (Case VII). Indeed, in the remaining cases renal function improved or returned to normal, usually in association with a fall in the serum calcium level and a regression of the granulomatous lesions. Similar evidence of the reversibility of the renal lesions in nephrocalcinosis has been observed in hyperparathyroidism following removal of a parathyroid adenoma[6] and in vitamin D intoxication following cessation of drug administration.[4] In at least one such case[4] resorption of subcutaneous calcium deposits occurred simultaneously, suggesting that the improvement in renal function

was due to a similar removal of precipitated calcium from the kidney. Since the deposition of calcium, which takes place chiefly in and about the tubules, is sooner or later followed by tubular destruction, interstitial fibrosis and glomerular atrophy and hyalinization,[31] it follows that the pothesis that the renal insufficiency was due to nephrocalcinosis, in view of Randall's[33] work showing that calculi have their origin in subepithelial calcium deposits.

It is of interest that, although the calcium deposits in the kidney in nephrocalcinosis are

TABLE II

ESSENTIAL CLINICAL FEATURES IN REPORTED CASES OF SARCOIDOSIS

Case* and Color	Age and Sex	Duration of Sarcoidosis before Renal Symptoms (yr.)	Polyuria, Frequency and/or Nocturia	Hyposthenuria (degree†)	Albuminuria (degree†)	Cylindruria (degree†)	Hematuria (degree†)	Pyuria (degree†)	Kidneys	Azotemia (degree†)	PSP Decreased (degree†)	Urea Clearance Decreased, (degree)
I, W	68, M	3	+	++	+	0	0	0	Normal size, no calcification or calculi	++	+++	.....
II, W	51, M	0	+	++	±	+	0	+	Bilateral renal calculi	+++	+	.....
III, W	30, M	0	+	+++	+	0	++	0	Calcified, contracted	++	.....	.....
IV, W	12, F	0	?+	+++	±	+	±	++	Pyelitis, rt. renal calulus (calcium oxalate)	+	++	+++
V, C	23, M	0	+	+++	±	±	±	0		++	++	++
VI, W	36, F	3	?+	.....	+§	?0	?0	?0	Right hydronephrosis and renal calculus (calcium oxalate)	++	+++	.....
VII, C	34, M	6	+	+	+	+§	+§	0	Bilateral pyelonephritis, nephrocalcinosis, and renal calculi, (urate)	+++	0	.....

* References

† Degree: 0 = absent, ± = slight or occasional, + = mild or few, ++ = moderate, +++ = marked.

§ Degree not stated.

?+ Presumably present on basis of associated symptoms, but not specifically mentioned in report.

?0 Not mentioned in published report and presumably absent.

Probable nephrocalcinosis:

Cases I and II—Present report

Case III—Schüpbach and Wernly[17] (Case 1)

Case IV—Van Creveld[18]

Case V—Klinefelter and Salley[19]

Case VI—Longcope and Freiman[14] (Case 13). Autopsied

Case VII—Longcope and Freiman[14] (Case 14)

Case VIII, Case IX } Longcope and Freiman[14]—M.G.H. case with hypercalcemia; no other data given

Case X—Zeldenrust[44]—case with hypercalcemia; no other data given

completeness of recovery following demineralization of the kidneys will be governed by the extent of these secondary changes.

At least nine instances of nephrolithiasis have been reported in sarcoidosis. (Table III.) In five of the seven in which the blood was examined hypercalcemia was found to be present. The serum calcium level in Case XXIII, which proved to be normal, was not investigated until almost two years after the stone had been passed so that an earlier elevation cannot be excluded. However in Case XIX repeated analyses failed to demonstrate hypercalcemia. Conceivably the stones were related to hypercalcuria in this case but since no urine analyses were carried out the etiology must remain in doubt. The occurrence of renal calculi in four of the seven cases with azotemia (Table III) is consistent with the hyusually composed largely of phosphates,[31] four of the five stones analyzed in this group were composed of calcium oxalate. (Table III.)

As might be expected, pyelonephritis complicated the nephrolithiasis in several instances but in only one (Case VII) did it appear to play a significant role in the development of renal failure. However, it may well have contributed to the renal symptoms in the others. It is of interest in this connection that many of the features of the renal picture in nephrocalcinosis are also seen in chronic pyelonephritis.[34]

Many of the symptoms commonly associated with hypercalcemia, such as muscular weakness, weight loss and gastrointestinal complaints, were seen in the group under consideration. However, it was difficult to distinguish between those related to hypercalcemia and those due to

the underlying sarcoidosis and complicating renal failure. The inordinate muscular weakness in Case I and the unusual dryness of the mouth in Case II were exceptions.

As for the underlying sarcoidosis in the group with renal failure, there were no distinctive features except possibly an unusually wide dissemination of the lesions. It is noteworthy that renal symptoms were evident at the very onset of the clinical manifestations of the disease in four of the seven cases (Cases II, III, IV and V), and dominated the clinical picture in three (Cases II, V and VII). Moreover, the renal failure and the disturbance in calcium metabolism was so suggestive of hyperparathyroidism in two cases (I and II) that surgical exploration of the neck was carried out. Similarly in the group with nephrolithiasis but without renal insufficiency (Table III), one patient was subjected to parathyroidectomy (Case XX). In these three cases hyperglobulinemia and bone cysts were lacking, illustrating the unreliability of these criteria in distinguishing between sarcoidosis and hyperparathyroidism. As subsequent events proved, the serum phosphate level was a more dependable diagnostic guide, but the presence of azotemia was thought to account for the absence of hypophosphatemia. To add to the diagnostic difficulties an atypical Bence-Jones protein was demonstrated in Case XX, a finding which has been noted in other cases of sarcoidosis.[12] Moreover, as illustrated in the recent report of Salmon,[35] not only may sarcoidosis simulate hyperparathyroidism but the reverse may occur when a parathyroid adenoma is accompanied by calcinosis of the lung.

No completely satisfactory explanation has been offered for the hypercalcemia in sarcoidosis. Certainly the lack of any direct correlation between the serum calcium level and the concentration of protein in the serum, the occurrence of hypercalcuria pointing to an increase in ionized calcium in the serum, and the well known fact that calcium is bound principally to albumin rather than to globulin,[36] would appear to exclude hyperglobulinemia as the cause. The possibility of parathyroid hyperplasia secondary to renal disease is suggested by the autopsy findings in Case VII and the osteoporosis noted in Cases I and IV; however, this explanation is highly improbable in view of the absence of hypophosphatemia in most cases of sarcoidosis

TABLE II (*Continued*)

WITH RENAL INSUFFICIENCY PROBABLY DUE TO NEPHROCALCINOSIS

Hypertension (degree)	Retinopathy	Cardiac Enlargement	Edema	Hypercalcuria	Serum Ca (range)	Serum P (range)	Ser. Alk. Phosph. (range)	Serum Prot. (range)	Serum Alb. (range)	Serum Glob. (range)	Bones	Metast. Calcification	Course of Renal Disease and Duration
0	0	0	0	+	15.0 11.5	5.2 4.9	5.3 ...	7.2 7.0	3.8 3.6	3.4 ...	Osteoporosis, fractures, no cysts	+	Slight improvement, 4 months
+	0	0	0	0	12.8 9.9	4.2 2.3	6.8 5.7	7.7 7.0	4.1 4.0	3.6 3.0	Normal, no cysts	0	Improved, one year
+++	0	0	0	+	16.3 11.2	5.8 3.3	4.0 2.7	....	...	...	Increased density, no cysts	+	Slight improvement, 9 years
+	..	0	++	+	15.6 10.9	3.7	2.9	9.1 5.8	4.1 3.5	4.6 2.0	Osteoporosis, no cysts	0	Improved, 3 years
0	‡	0	0	+	17.4 13.0	4.3 4.0	N	10.5	? 3.0	? 5.2	Normal, no cysts	0	? Cure in 17 months
?0	?0	++	?0	+	15.5 9.9	4.7 2.5	5.2 2.6	12.5 7.0	4.8 3.2	7.8 4.3	Normal, cyst in finger later	0	Apparent cure renal failure 2 yr.; stone removed 6 yr. later
0	?0	0	?0	..	16.5	6.1	...	7.6	3.4	3.2	? Cyst of finger	0	Died in uremia in less than one yr.

‡ Sarcoidal lesions of retina.

Possible nephrocalcinosis:

Case XI—Salvesen[45] (Case 2)

Case XII—Horton, Lincoln and Pinner (Case 1). Autopsied

Case XIII—Ustvedt[46] (Case 2)

Case XIV—Ustvedt[46] (Case 3)

Case XV—Rotenberg and Guggenheim[32]

Case XVI—Longcope and Freiman;[14] no data given

Massive invasion of kidneys:

Case XVII—Chanials.[38] Autopsied

Vascular disease of kidneys:

Case XVIII—Ricker and Clark[27] (Case 9). Autopsied

with hypercalcemia[12] and the demonstration of normal parathyroids in at least three (Cases I, II, XX). As pointed out in the discussion of Case I, the most logical explanation for the hypercalcemia and demineralization of the bones would appear to be invasion of the bone marrow by granulomatous lesions, which are often surrounded by masses of osteoclasts suggesting bone resorption,[23] despite the difficulty in demonstrating these sarcoid lesions roentgenologically in some cases. However, the results of a calcium balance study carried out in Case VI* by Albright and Reifenstein[6] have been offered as evidence that the hypercalcemia in sarcoidosis is probably due not to a primary disturbance in bone but rather to some fundamental change in the blood leading to an increase in its calcium content.[14] On an intake of 360 mg. of calcium the patient excreted 2,560 mg., exhibiting a negative calcium balance of 2,200 mg. When the intake was raised to 2,900 mg., the excretion of calcium increased to only 3,460 mg., thereby reducing the negative balance to 560 mg. In short, increasing the calcium intake appeared to decrease the loss of calcium from bone, a phenomenon said not to occur in primary bone disorders accompanied by a negative calcium balance.[14] Obviously further studies of this kind are needed to define more clearly the nature of the disturbance in calcium metabolism in sarcoidosis. If indeed the disturbance is only a secondary manifestation, reflecting a more fundamental metabolic disturbance affecting the composition of the blood, there are no clues as to its nature. However, such factors as alterations in citrate metabolism, which are known to affect calcium mobilization and excretion,[37–39] have not been investigated.

TABLE III

REPORTED CASES OF NEPHROLITHIASIS IN SARCOIDOSIS

Case*	Author and Reference	Azotemia	Hypercalcemia	Type of Stone	Side	Complications
II	Klatskin and Gordon	+	+	?	Bilateral	
IV	Van Creveld[18]	+	+	Calcium oxalate	Unilateral	Chronic pyelitis
VI	Longcope and Freiman (Case 13)[14]	+	+	Calcium oxalate	Unilateral	Hydronephrosis
VII	Longcope and Freiman (Case 14)[14]	+	+	Urate	Bilateral	Chronic pyelonephritis
XIX	Longcope and Freiman (M. G. H. case)[14]	0	0	Calcium oxalate	?	
XX	Albright and Reifenstein (Case 6)[6]	?	+	Calcium oxalate	Bilateral	Chronic pyelitis
XXI	Salvesen (Case 1)[45]	?	?	?	Unilateral	
XXII	Roos[47]	?	?	?	Unilateral	Enlarged kidneys
XXIII	Spencer and Warren[48]	0	0	?	Unilateral	

* Same numbering system as in Table II.

Albright and Reifenstein[6] and Longcope and Freiman[14] have both described the cases of sarcoidosis with renal complications seen at the Massachusetts General Hospital; care was taken to avoid duplication of cases by comparing the individual protocols in each report.

It is evident from the cases presented that sarcoidosis can lead to serious renal injury. Since this appears to be related to an increase in serum calcium, an effort should be made to detect impairment of renal function as early as possible in all cases with hypercalcemia, and to institute measures to lower the serum calcium level. The evidence presented suggests that simple reduction of the calcium intake and increasing the consumption of water are at least partially effective. However, control of the granulomatous process would appear to be the more logical approach, since the serum calcium level tends to fall as the activity of the disease subsides. Recent reports of the effectiveness of ACTH and cortisone in producing at least temporary remissions in the disease[40–43] offers some hope of controlling and possibly of preventing renal complications.

* The values cited are taken from Longcope and Freiman's paper[14] and differ slightly, but not significantly, from those in Albright and Reifenstein's monograph.[6] The former were chosen because more complete data were given.

SUMMARY

Two cases of sarcoidosis with hypercalcemia and renal failure are presented. Metastatic calcification was present in one and renal stones in the other. On the basis of the findings in these and similar cases found in the literature, the suggestion is made that the renal failure seen in hypercalcemic sarcoidosis is due to nephrocalcinosis.

The difficulty in distinguishing between sarcoidosis and hyperparathyroidism, especially when accompanied by renal failure, is emphasized, and the mechanisms underlying the development of hypercalcemia in sarcoidosis are discussed.

REFERENCES

1. Albright, F., Baird, P. C., Cope, O. and Bloomberg, E. Studies of the physiology of the parathyroid glands. IV. Renal complications of hyperparathyroidism. *Am. J. M. Sc.*, 187: 49, 1934.
2. Elsom, K. A., Wood, F. C. and Ravdin, I. S. Hyperparathyroidism with renal insufficiency. *Am. J. M. Sc.*, 191: 49, 1936.
3. Tumulty, P. A. and Howard, J. E. Irradiated ergosterol poisoning. Report of two cases. *J. A. M. A.*, 119: 233, 1942.
4. Danowski, T. S., Winkler, A. W. and Peters, J. P. Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis. *Ann. Int. Med.*, 23: 22, 1945.
5. Howard, J. E. and Meyer, R. J. Intoxication with vitamin D. *J. Clin. Endocrinol.*, 8: 895, 1948.
6. Albright, F. and Reifenstein, Jr., E. C. The Parathyroid Glands and Metabolic Bone Disease. Selected Studies. Baltimore, 1948. The Williams & Wilkins Co.
7. Herrmann, J. B., Kirsten, E. and Krakauer, J. S. Hypercalcemic syndrome associated with androgenic and estrogenic therapy. *J. Clin. Endocrinol.*, 9: 1, 1949.
8. Meachem, G. C. and Heinle, R. W. Association of high ionized serum calcium with renal failure in plasma cell myeloma. *Tr. Am. Soc. Clin. Investigation*, May 1, 1950.
9. Albright, F., Burnett, C. H., Cope, O. and Parson, W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. *J. Clin. Endocrinol.*, 1: 711, 1941.
10. Burnett, C. H., Commons, R. R., Albright, F. and Howard, J. E. A syndrome characterized by hypercalcemia, calcinosis, and renal insufficiency following prolonged intake of calcium and alkali. *J. Clin. Endocrinol.*, 8: 584, 1948.
11. Burnett, C. H., Commons, R. R., Albright, F. and Howard, J. E. Hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis, and renal insufficiency. *New England J. Med.*, 240: 787, 1949.
12. Harrell, G. T. and Fisher, S. Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcum and phosphatase values. *J. Clin. Investigation*, 18: 687, 1939.
13. Freiman, D. G. Sarcoidosis. *New England J. Med.* 239: 664, 709, 743, 1948.
14. Longcope, W. T. and Freiman, D. G. A study of sarcoidosis based on a combined investigation of 160 cases including 30 autopsies from the Johns Hopkins Hospital and Massachusetts General Hospital. *Medicine*, 31: 1, 1952.
15. Horton, B., Lincoln, H. S. and Pinner, M. Noncaseating tuberculosis: case reports. *Am. Rev. Tuberc.*, 39: 186, 1939.
16. Van Rijssel, Th. G. De Ziekte. Cited by Longcope and Freiman.[14]
17. Schüpbach, A. and Wernly, M. Hyperkalzaemie und Organverkalkungen bei Boeckschen Krankheit. *Acta med. Scandinav.*, 115: 401, 1943.
18. Van. Creveld, S. Disturbance of the metabolism in Besnier-Boeck's disease. *Ann. Paediat.*, 157: 1, 1941.
19. Klinefelter, H. F., Jr. and Salley, S. M. Sarcoidosis simulating glomerulonephritis. *Bull. Johns Hopkins Hosp.*, 79: 333, 1946.
20. Walsh, F. B. and Howard, J. E. Conjunctival and corneal lesions in hypercalcemia. *J. Clin. Endocrinol.*, 7: 644, 1947.
21. Barney, J. D. and Sulkowitch, H. W. Progress in the management of urinary calculi. *J. Urol.*, 37: 746, 1937.
22. Shinowara, G. Y., Jones, L. M. and Reinhart, H. L. The estimation of serum inorganic phosphate and "acid" and "alkaline" phosphatase activity. *J. Biol. Chem.*, 142: 921, 1942.
23. Schaumann, J. Notes on the histology of the medullary and osseous lesions in benign lymphogranuloma and especially on their relationship to the radiographic picture. *Acta radiol.*, 7: 358, 1926.
24. Robert, F. Cited by Longcope and Freiman.[14]
25. Ellsworth, R. and Howard, J. E. Studies on the physiology of the parathyroid glands. V. Some responses of normal human kidneys and blood to intravenous parathyroid extract. *Bull. Johns Hopkins Hosp.*, 55: 296, 1934.
26. Klatskin, G. and Yesner, R. Hepatic manifestations of sarcoidosis and other granulomatous diseases. *Yale J. Biol. & Med.*, 23: 207, 1950.
27. Ricker, W. and Clark, M. Sarcoidosis. A clinicopathologic review of three hundred cases, including twenty-two autopsies. *Am. J. Clin. Path.*, 19: 725, 1949.
28. Chanials. Cited by Schüpbach and Wernly.[17]
29. Garland, H. G. and Thompson, J. G. Uveo-parotid tuberculosis (febris uveoparotidea of Heerfordt). *Quart. J. Med.*, 2: 157, 1933.
30. Staehelin, H. R. Zur Frage der Besnier-Boeckschen Krankheit und der Periarteritis nodosa. *Virchow's Arch.*, 309: 235, 1942.
31. Anderson, W. A. D. (*a*) The renal lesion in hyperparathyroidism. *Endocrinology*, 24: 372, 1939. (*b*) Hyperparathyroidism and renal disease. *Arch. Path.*, 27: 753, 1939.
32. Rotenberg, L. and Guggenheim, A. Boeck's sarcoid (report of a case with renal involvement). *Dis. of Chest*, 8: 392, 1942.
33. Randall, A. The origin and growth of renal calculi. *Ann. Surg.*, 105: 1009, 1937.
34. Longcope, W. T. and Winkenweider, W. L.

Clinical features of the contracted kidney due to pyelonephritis. *Bull. Johns Hopkins Hosp.*, 53: 255, 1933.

35. Salmon, H. W. and Maynell, G. G. Primary hyperparathyroidism (adenoma) simulating sarcoidosis. Report of a case. *Brit. M. J.*, 2: 1440, 1951.
36. Gutman, A. B. and Gutman, E. B. Relation of serum calcium to serum albumin and globulins. *J. Clin. Investigation*, 16: 903, 1937.
37. Gomori, G. and Gulyas, E. Effect of parenterally administered citrate on the renal excretion of calcium. *Proc. Soc. Exper. Biol. & Med.*, 56: 226, 1944.
38. Chang, T. S. and Freeman, S. Citric acid and its relation to serum and urinary calcium. *Am. J. Physiol.*, 160: 330, 1950.
39. Freeman, S. and Chang, T. S. (*a*) Role of the kidney and of citric acid in production of transient hypercalcemia following nephrectomy. *Am. J. Physiol.*, 160: 335, 1950. (*b*) Effect of thyroparathyroidectomy and vitamin D upon serum calcium and citric acid of normal and nephrectomized dogs. *Am. J. Physiol.*, 160: 341, 1950.
40. Sones, M., Israel, H. L., Dratman, M. B. and Frank, J. H. Effect of cortisone in sarcoidosis. *New England J. Med.*, 244: 209, 1951.
41. Small, M. J. Favorable response of sarcoidosis to cortisone treatment. *J. A. M. A.*, 147: 932, 1951.
42. Siltzbach, L. E. Effects of cortisone in sarcoidosis. A study of thirteen patients. *Am. J. Med.*, 12: 139, 1952.
43. Renold, A. E., Forsham, P. H., Maesterrena, J. and Thorn, G. W. Intravenously administered ACTH. A preliminary report. *New England J. Med.*, 244: 796, 1951.
44. Zeldenrust. Cited by Van Creveld.[18]
45. Salvesen, H. A. The sarcoid of Boeck, a disease of importance to internal medicine. Report on four cases. *Acta med. Scandinav.*, 86: 127, 1935.
46. Ustvedt, H. J. Omkring det Boeck'ske sarkoids nosografi og diagnose. *Nord. med.*, 2: 1677, 1939.
47. Roos, B. Über das Vorkommen der Schaumannschen benignen Lymphogranulomatose (des Boeckschen benignen Miliarlupoids). *Ztschr. f. Kinderheilk.*, 59: 280, 1937.
48. Spencer, J. and Warren, S. Boeck's sarcoid. Report of a case, with clinical diagnosis confirmed at autopsy. *Arch. Int. Med.*, 62: 285, 1938.

The Physiologic Evaluation and Management of Chronic Bone Marrow Failure*

VIRGIL LOEB, JR., M.D., CARL V. MOORE, M.D. *and* REUBENIA DUBACH, PH.D.
St. Louis, Missouri

WITH technics currently available the erythropoietic equilibrium in patients with diseases characterized by failure of bone marrow function can be evaluated by measuring rates of red cell production and destruction. In ten patients studied with these methods it has been possible to demonstrate: (1) that increased destruction of erythrocytes was partly responsible for the anemia in some instances; and (2) that cortisone or ACTH administration occasionally increased the rate of erythrocyte formation. When splenectomy was performed under these circumstances, partial to marked clinical improvement occurred because the hemolytic component of the anemia was corrected and/or erythropoiesis was accelerated. The latter result provides evidence to indicate that an abnormally functioning spleen may depress the marrow. The present report describes the application of this physiologic evaluation of erythropoietic equilibrium in the clinical management of ten patients. It is emphasized that splenectomy was performed only after extensive study, and only after increased hemolysis or marrow stimulation by cortisone or ACTH had been demonstrated; there is no intent to recommend splenectomy routinely in the treatment of bone marrow failure.

Part of the confusion existing at the present time concerning the hematologic changes which characterize the anemia of chronic primary bone marrow failure stems from the varied terminology encountered in the literature on this subject. The term "aplastic anemia" originally used by Ehrlich[1] to describe total absence of hematopoietic tissue in the bone marrow has subsequently been applied to many situations in which marrow cellularity varies from aplasia to hyperplasia.[2,3] In 1938 Rhoads and Miller[4] emphasized the variation in appearance of the bone marrow in aplastic anemia; subsequently Bomford and Rhoads[5] used the term "refractory anemia" to include "idiopathic primary anemias responding only to transfusions" in which divergent degrees of marrow cellularity were encountered.

The concept of failure of bone marrow function as the underlying physiologic change in the pathogenesis of this condition has been stressed repeatedly in the literature. The phrase "bone marrow failure" was introduced in 1904 by Vaquez and Aubertin.[6] Ten years later Frank[7] postulated that aplastic anemia was due to deficient hematopoietic function. Subsequent reviews by Lescher and Hubble,[8] Thompson et al.,[9] Middleton and Meyer,[10] Vaughan[11] and Wyatt and Sommers[12] have pointed out that a disturbance in bone marrow function may exist which cannot be correlated with bone marrow morphology. The first physiologic measurements of the decrease in erythropoietic function in "hypoplastic anemia" were reported in 1946 by Dubach, Moore and Minnich.[13] Measurement of the utilization of intravenously injected radioactive iron for hemoglobin synthesis demonstrated that red blood cell production was markedly impaired. Subsequent reports[14,15] have corroborated and expanded these observations.

Since the erythropoietic equilibrium depends not only on the rate of erythrocyte production but also on the rate of erythrocyte destruction, the present study was undertaken to evaluate the relative importance of these two factors in patients with chronic primary bone marrow

* From the Department of Internal Medicine, Washington University School of Medicine, St. Louis, Mo. Presented in part before the Twenty-fourth Annual Meeting of the Central Society for Clinical Research, Chicago, November 2, 1951. This investigation was supported by Research Grant No. G-2806 from the National Institutes of Health, U. S. Public Health Service. It was carried out during the tenure of a Damon Runyon Clinical Research Fellowship recommended by the Committee on Growth of the National Research Council and administered by the American Cancer Society, Inc.

failure. Data derived from determination of the red blood cell count, hemoglobin level, reticulocyte count, efficiency of radioactive iron utilization, and examination of the bone marrow provided information concerning erythropoiesis in the individual cases. The presence or absence of a hemolytic component was detected by measurement of hemoglobin catabolism as reflected by the fecal urobilinogen excretion and the calculated hemolytic index, and by determination of the survival time of transfused red blood cells.

METHODS

Patients were observed and followed in the Washington University Hematology Clinic and the Barnes Hospital. Peripheral blood counts were made with counting chambers and pipettes standardized by the U. S. Bureau of Standards. Dameshek's method[16] was used for reticulocyte and platelet counts. Hemoglobin was measured as oxyhemoglobin in an Evelyn photoelectric colorimeter. Blood films were stained supravitally and with Wright's stain. Bone marrow preparations were studied with supravital stain, Wright's stain and by tissue section of a marrow clot. Aspirations were made from the sternum, iliac crest and/or vertebral spinous process. When insufficient tissue was obtained, surgical marrow biopsy was performed. Daily fecal urobilinogen excretion was determined in a four-day pooled specimen, using the technic of Watson.[17] The hemolytic index was calculated according to the method of Miller and associates.[18] The modified Ashby technic of Dacie and Mollison[19] was used for the estimation of red blood cell survival times. Determination of the utilization of intravenously injected radioactive iron for hemoglobin synthesis was carried out according to the procedure used in this laboratory as previously described.[13] From 5 to 15 mg. of radioactive iron were injected in the form of ferrous ascorbate. The amount of Fe^{59} injected was equivalent to approximately 1,000,000 counts per minute. According to this method, in the normal healthy individual at least 75 per cent of the injected tracer dose of radioactive iron can be accounted for in the erythrocytes of the peripheral blood in two weeks. Serum iron levels were determined by the method of Moore[20] and the iron binding capacity of the serum was measured by a modification of the technic of Rath and Finch.[21]

CASE REPORTS AND OBSERVATIONS

Primary Erythroid Hypoplasia (Anerythrocytic Anemia; Erythrocytogenesis imperfecta, etc.)

Two of the patients who responded most dramatically to splenectomy were brothers in whom there was an extreme degree of erythroid hypoplasia in the bone marrow. In the older of these two patients red cell destruction was accelerated and an erythrogenic stimulatory effect of cortisone and ACTH was demonstrated.

CASE 1. E. H.* (B. H. No. 121563) was first noted to have anemia in 1945 at age seventeen. (Fig. 1.) His red cell count was then 2,300,000 per cu. mm. with 6.5 gm. of hemoglobin per 100 cc. Bone marrow aspiration and biopsy revealed almost complete absence of erythropoietic elements; myeloid cells and megakaryocytes were plentiful and there was a moderate increase in the number of reticulum cells, plasma cells and lymphocytes. No history of exposure to known bone marrow toxin could be elicited by detailed questioning or by direct inspection of the home. A diagnosis of idiopathic primary hypoplastic anemia was made. From 1945 to March, 1950, the patient was treated with a total of 526 whole blood transfusions of 500 cc. each. These were given when necessary in order to maintain a level of red cells between 2,500,000 and 3,000,000. During these years repeated bone marrow examinations revealed selective absence of erythroid elements; the reticulocyte levels remained between 0.0 and 0.5 per cent. Moderate granulocytopenia and thrombocytopenia were present throughout this period and the erythrocytes varied considerably in size and shape. As transfusion therapy was continued, the skin assumed a gray-brown color, and the spleen and liver became palpably enlarged. Although no evidence of hemolysis was noted when the patient first came under observation, a hemolytic component to the anemia became manifest and during the latter part of 1949 it became necessary to give more frequent transfusions in order to maintain a comfortable red cell level.

In March, 1950, the patient was re-evaluated because of the necessity for transfusions approximately three times weekly and the troublesome reactions with most of these. Evidence in favor of decreased red cell production was

* A preliminary report of this patient has been published elsewhere.[22]

derived from: (1) the history; (2) the lack of nucleated red blood cells in the bone marrow; (3) reticulocytopenia; and (4) a radioactive iron utilization study which accounted for less than 4 per cent of the injected dose in six weeks. Increased hemolysis was detected by: (1) the need for frequent transfusions; (2) a daily fecal urobilinogen excretion of 200 mg. with a hemolytic index of 52; and (3) a survival time of thirty-five days for normal erythrocytes transfused into the patient. The Coombs test was negative. On March 30, 1950, ACTH was started in a dosage of 100 mg. daily, administered in four divided intramuscular injections. On the eleventh day of treatment the reticulocytes began to rise and five days later reached a peak of 22 per cent. During the height of the reticulocyte response the bone marrow aspiration showed a striking change, with marked erythroid hyperplasia without maturation arrest. ACTH therapy was discontinued and the reticulocytes fell to their previous low level; the bone marrow at this time showed partial reversion to erythroid hypoplasia. On May 15th the patient's spleen was removed. It weighed 650 gm. and microscopic examination showed extensive hemosiderosis; liver biopsy revealed a similar increase in iron deposition without fibrosis or other evidence of liver damage. Eight days after the operation a second reticulocyte response occurred which reached a peak of 23 per cent. Bone marrow aspiration, performed during the height of the reticulocytosis, again showed a striking erythroid hyperplasia. The patient's red cell and hemoglobin values remained at a constant high level for the next two and a half months with normal reticulocyte counts. During the first part of August, 1950, the red cells and hemoglobin began to decrease slowly and bone marrow examination revealed evidence of erythroid hypocellularity. A second course of ACTH, given in smaller dosage, induced no significant change in the peripheral blood values. In the middle of September a total of 3,500 cc. of whole blood was administered; the red count then fell slowly over the next three months to the original level. An Ashby survival study showed a normal life span of transfused erythrocytes and the fecal urobilinogen excretion was within normal limits.

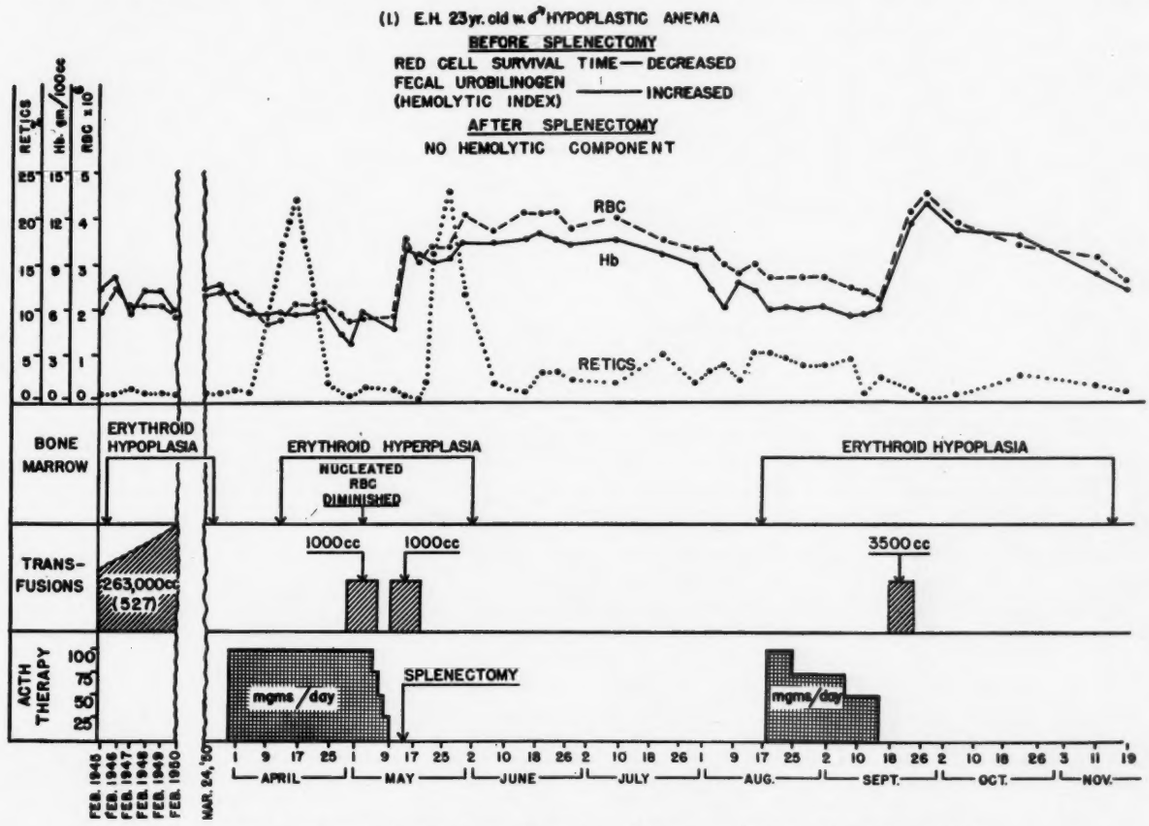


FIG. 1. Case 1. Hematologic observations from February, 1945 to November, 1950.

In December, 1950, the patient was started on cortisone, during which time there was a moderate reticulocyte elevation to 11 per cent and reversion of the bone marrow to normal cellularity. The red count did not rise, however, and in February, 1951, 4,000 cc. of blood were transfused. Cortisone was continued until July 26, 1951. From the time of the last transfusion until the present (24 months) the red cell count, hemoglobin level and reticulocytes have remained within the normal range. The bone marrow appears normally cellular without alteration of the erythroid elements; a radioactive iron study repeated in February, 1951, showed 28 per cent utilization in three weeks. Even though cortisone was discontinued, the patient has required no further transfusions or adrenocortical hormone therapy. He feels perfectly well at the present time and is able to carry out the duties of a fireman. The only stigmata of his illness are the cutaneous evidence of hemosiderosis, the enlarged liver and a serum iron level of 300 μg. per 100 cc. with total saturation of the iron-binding protein. (Fig. 2.)

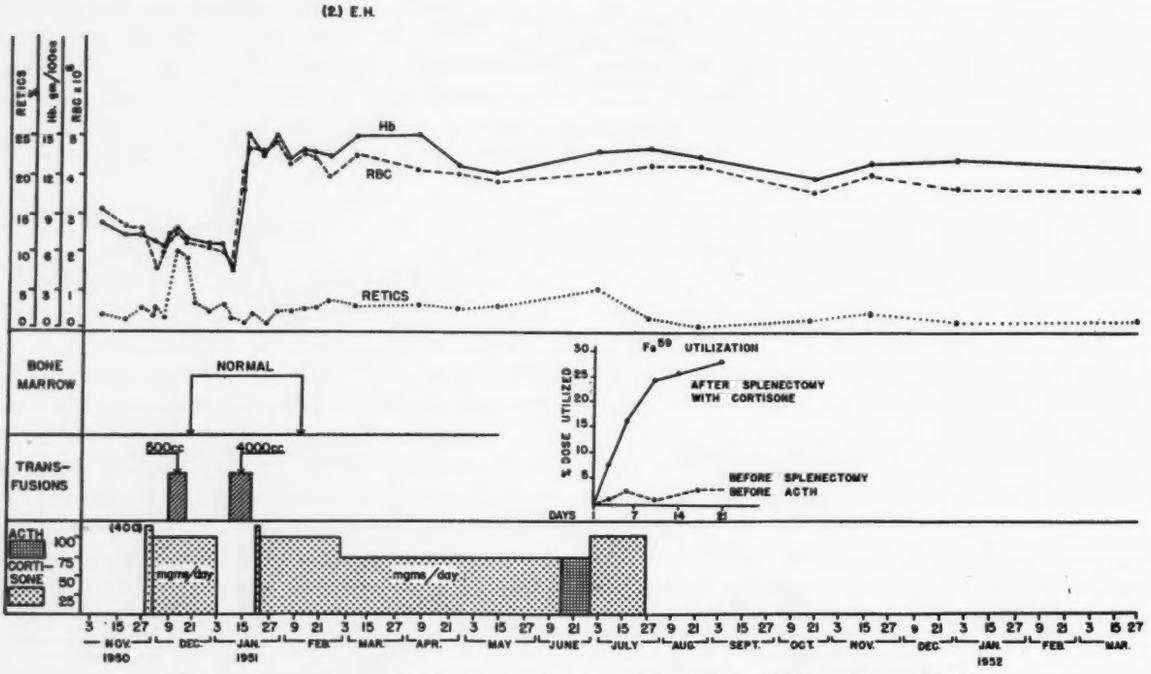


FIG. 2. Case I. Hematologic observations from November, 1950 to March, 1952.

CASE II. L. H. (B. H. No. 163483), the brother of E. H., was first seen in September, 1948, complaining of weakness and easy fatigability. (Fig. 3.) He was seventeen years of age. Initial laboratory data revealed a red blood cell count of 1,710,000 per cu. mm., 6.0 gm. of hemoglobin per 100 cc., white blood count 5,000, platelets 185,000 and reticulocytes 0.0 per cent. Anisocytosis and poikilocytosis of the red cells were marked. Several bone marrow aspirations taken from various sites showed erythroid hypoplasia with otherwise normally cellular marrow. No underlying cause for the hypoplastic anemia could be elicited. Transfusions were administered at regular intervals in order to maintain a red cell count of around 3,000,000. A radioactive iron study revealed only 5 per cent utilization for hemoglobin synthesis in nineteen days. From September, 1948, until July, 1950, the patient received a total of sixty-one whole blood transfusions of 500 cc. each. During a four-month period in the summer of 1949 he failed to return to the clinic and the red cell count fell to 1,000,000 with 3.0 gm. of hemoglobin. In July, 1950, a life span of ninety days for normal erythrocytes transfused into the patient was demonstrated by the Ashby technic. Fecal urobilinogen excretion at this time was 65 mg. per day with a hemolytic index of 10. Bone marrow examination again presented evidence of selective absence of erythroid elements.

Because of the gratifying response of the patient's brother (E. H.), splenectomy was done on September 23, 1950; the last blood transfusion was given on the following day. The spleen weighed 260 gm. and extensive hemo-

siderosis could be demonstrated throughout the sections; no other abnormalities were noted. Following the operative procedure the reticulocytes began to rise and reached a maximum of 11 per cent in approximately three weeks. Five days after the removal of the spleen a bone transfusion therapy alone and developed the usual complications of hemosiderosis and hepatosplenomegaly. Coincident with the latter a hemolytic component became manifest. The administration of ACTH evoked a striking erythropoietic response, characterized by reticu-

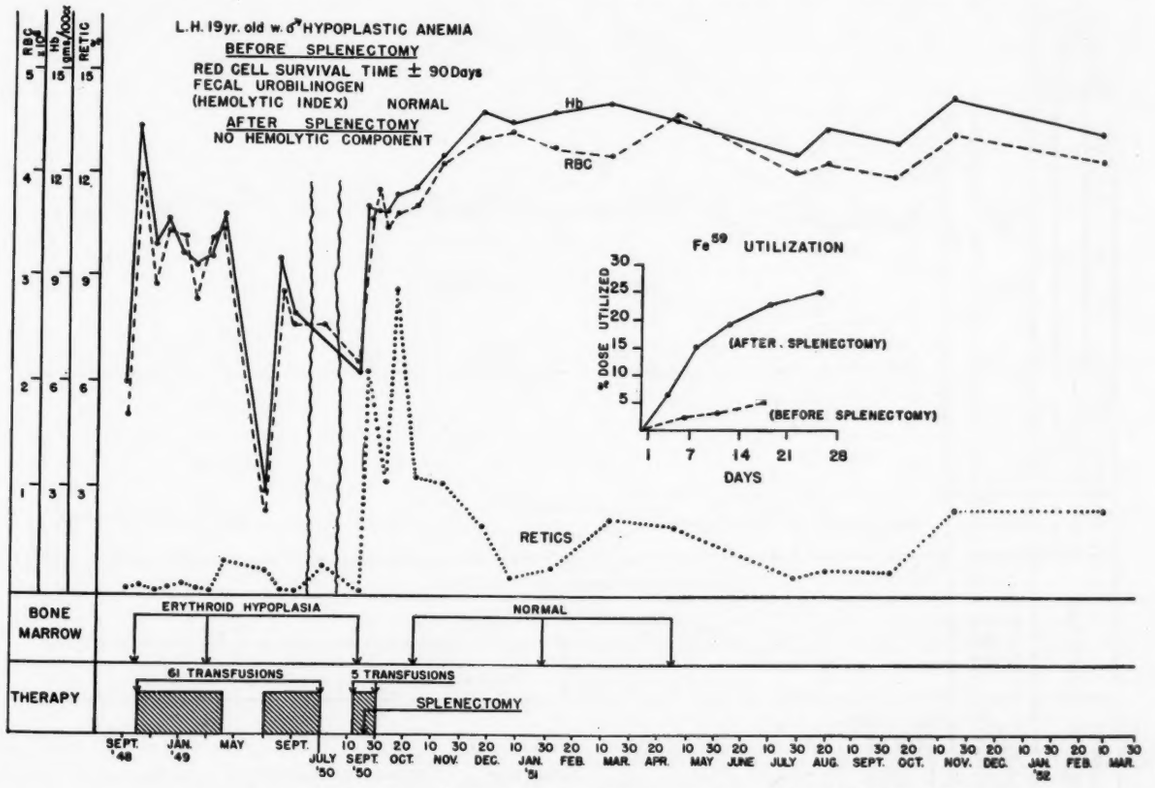


FIG. 3. Case II. Hematologic observations from September, 1948 to March, 1952.

marrow aspiration appeared normally cellular with a 2:1 myeloid:erythroid ratio. The patient has required no further transfusions since the operation (29 months) and his red cell and and hemoglobin values have remained at normal levels. A repeat radioactive iron utilization study carried out shortly after splenectomy accounted for 26 per cent of the injected dose in four weeks. The patient remains well at the present time without evidence of hematologic abnormality and is able to engage in the activities of a professional ice skater.

Comment: Over a period of five years the bone marrow in E. H. (Case I) showed evidence of a severe degree of selective hypoplasia of the erythroid elements. The term "anerythropoietic anemia" as suggested by Middleton[10] could be applied to this case; other examples of "pure red cell anemia" have been recognized for many years.[8,23–26] The patient was maintained on locytosis and conversion of the bone marrow to normal. It was only after the latent ability of the bone marrow to produce red blood cells had been demonstrated that removal of the spleen was advocated. Splenectomy was followed by immediate cessation of the excessive hemolysis and transient bone marrow recovery ensued. Subsequently, it was again necessary to administer cortisone for several months to promote erythropoiesis but the patient has now maintained normal blood and bone marrow findings for nineteen months after stopping cortisone, twenty-four months after his last transfusion, and thirty-three months after splenectomy. The change to normal erythropoiesis after five years of erythrocytic hypoplasia was unexpected and has been dramatic.

Patient L. H. (Case II) had an anemia characterized by failure of erythropoiesis without definite evidence of a hemolytic component.

The description of familial hypoplastic anemia of childhood as reported by Estren and Dameshek[27] might be applied to these two cases except for the fact that reticulocytopenia was consistently found in E. H. and L. H. before therapy. Splenectomy was followed by apparently complete recovery of the bone marrow with restoration of erythropoiesis, which has now lasted over twenty-nine months.

Other examples of a beneficial effect from splenectomy in somewhat similar cases of anerythrocytic anemia have been reported.[24,26–28]

Myelosclerosis

Two patients with myelosclerosis showed increased erythrogenesis while taking cortisone. A severe hemolytic component was completely relieved by splenectomy in one individual and the second patient has continued to do well on maintenance cortisone therapy.

Case III. G. R.* (B. H. No. 151708), a woman fifty-four years of age, had always enjoyed excellent health until 1947 when she became easily fatigued and noticed pallor. (Fig. 4.) Laboratory data at that time revealed a red count of 2,890,000 per cu. mm., hemoglobin 6.4 gm. per 100 cc., white blood count 4,450, platelets 260,000, reticulocytes 3.4 per cent and a differential showing occasional myelocytes and nucleated red blood cells in the peripheral blood. The erythrocytes were characterized by marked variation in size and shape. Several attempts to aspirate bone marrow from multiple sites failed to yield any hematopoietic tissue; the clinical impression was myelophthisic anemia presumably due to myelosclerosis. This was subsequently confirmed by surgical biopsy of the sternum; it was noted that active marrow substance could be found within the densely fibrotic tissue. During the latter part of 1947 the patient received her first blood transfusions; these were repeated when indicated in order to maintain a red cell count of about 3,500,000. From November, 1947, to March, 1950, she

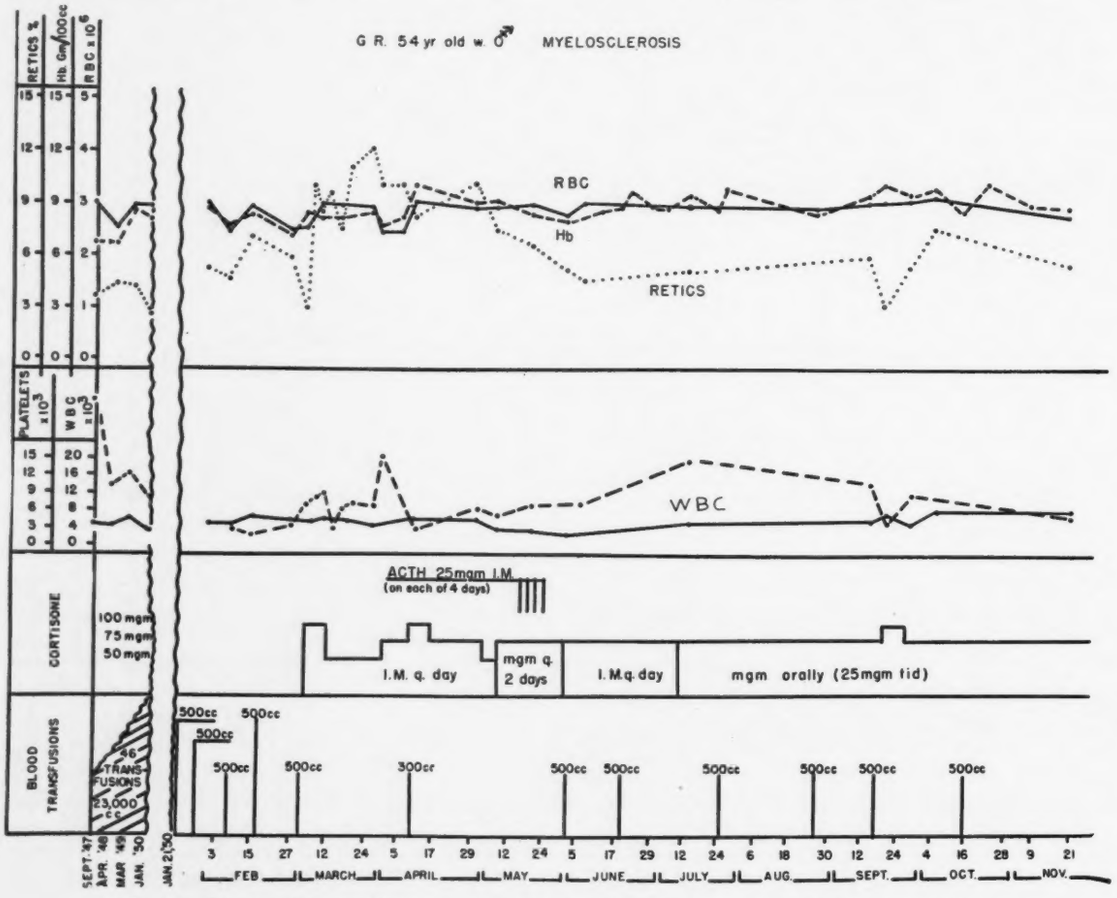


Fig. 4. Case III. Hematologic observations from September, 1947 to November, 1950.

* A preliminary report of this patient has been published elsewhere.[22]

received fifty whole blood transfusions of 500 cc. each; these were given with increasing frequency. When the patient was first seen in 1947 her spleen was not palpable but as the disease progressed and transfusions were continued splenomegaly became obvious and the skin liver was easily palpable. Cortisone was discontinued in June, 1951, and four transfusions were necessary in the next month. On July 30, 1951, a 1,550 gm. spleen was removed. Microscopic examination revealed extensive extramedullary hematopoiesis and hemosiderosis; a liver biopsy

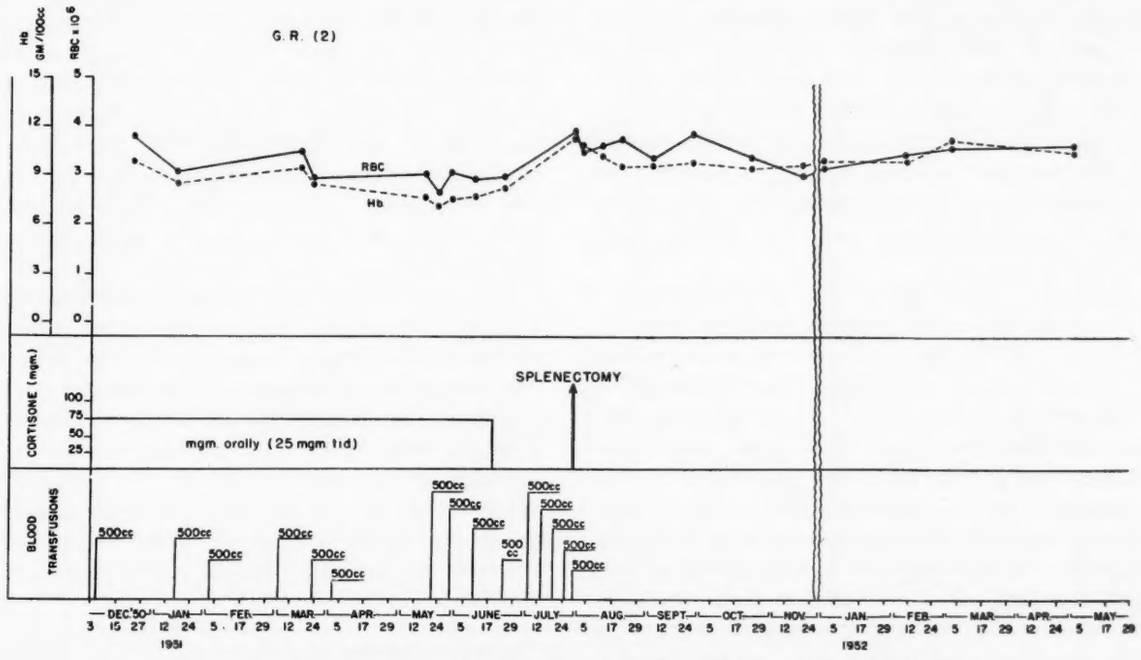


FIG. 5. Case III. Hematologic observations from December, 1950 to May, 1952.

assumed a gray-brown color. During 1949 an Ashby survival study showed a life span of approximately ninety days for transfused normal erythrocytes. On March 6, 1950, cortisone therapy was instituted and continued for fifteen months until June, 1951. During the initial period of cortisone administration her transfusion requirement decreased from approximately three transfusions per month to one every five to six weeks. A sustained reticulocytosis was apparent during the first three months, following which the reticulocytes returned to their previous level. (Fig. 5.) She continued to do well during the rest of 1950 and the early part of 1951 but in April, 1951, she began to require more frequent transfusions in order to maintain a comfortable red cell level and a hemolytic component to the anemia became manifest. An Ashby survival study repeated in May, 1951, showed a life span of only thirty days for normal cells transfused into the patient. The Coombs test was negative. By this time the patient's spleen had enlarged to 15 cm. below the left costal margin and the presented the same appearance. Following the operation the patient has required no further transfusions or cortisone therapy (nineteen months); she continues to feel well and is able to engage actively in her profession. The red cell count has remained between 3,500,000 and 4,000,000 with 10–11 gm. per cent hemoglobin.

Comment: Splenectomy was recommended for this patient because it was obvious that the hemolytic component of the anemia was of such great severity that her life was in serious jeopardy. The administration of cortisone had resulted in a decrease in the need for transfusions over a period of fifteen months but subsequently the patient began to hemolyze transfused red cells at a rapid rate. The diagnosis of myelosclerosis has been considered a contraindication to splenectomy since Donhauser's original description in 1908[29] but the circumstances in this case were such that there was a rational basis for such a procedure. Because of the increased red cell destruction and the erythropoietic response to cortisone, and because microscopic examination of the bone marrow

biopsy revealed foci of myelopoiesis and erythropoiesis in the sclerotic medullary space, there was reason to anticipate a beneficial effect from removal of the spleen. Since this was done the patient has not only been free of hemolysis but has also required no further cortisone or transfusions in the nineteen months that have elapsed. Andersen and Sørensen[30] have reported a case of myelosclerosis responding well to splenectomy, and Edwards[31] removed the spleen from a similar patient with a hemolytic component who did well during the two year follow-up period. Franks[32] has also reported a patient who improved following splenectomy but the patient had been observed for only one month after the operation.

Case IV. O. D. (B. H. No. 205781), a forty-seven year old white woman, was first seen in February, 1952. She had noticed enlargement of the left upper quadrant of the abdomen in 1946 and had complained of easy bruising and intermittent bone pain since that time. The patient had helped paint her house on several occasions and had used a paint remover containing benzene. She was seen by her physician in 1946 at which time sternal marrow aspiration was reported to show slight diminution of erythroid cells. A tentative diagnosis of myeloid metaplasia of the spleen was made. Several transfusions were given then and repeated in 1947. She was followed by her own physician from 1948 until 1951. Sporadic episodes of purpura were noted and during the latter part of 1951 increasing weakness and epistaxis developed. Her spleen was found to extend 13 cm. below the left costal margin. Laboratory data in January, 1952, revealed a red cell count of 4,320,000, hemoglobin 11.7 gm., reticulocytes 1.9 per cent, white blood count 5,750, and 39,000 platelets per cu. mm. The differential count indicated myeloid immaturity with 51 per cent segmented neutrophils, 5 per cent band forms, 4 per cent metamyelocytes, 12 per cent myelocytes, 1 per cent basophils, 20 per cent lymphocytes and 7 per cent monocytes; there was marked anisocytosis and poikilocytosis of the erythrocytes. Several bone marrow aspirations failed to yield adequate clumps of marrow tissue and a surgical bone marrow biopsy was obtained. Histologic examination of the sections indicated advanced myelosclerosis. The patient was given 100 mg. of cortisone daily by mouth; there was a progressive rise in the platelet count to normal, a reticulocyte elevation to 13 per cent and a rise in the white blood count to 15,000. Red cell and hemoglobin values remained around 5,000,000 with 14.5 gm. hemoglobin. The patient was discharged from the hospital in February, 1952, and continued taking cortisone at home. The peripheral blood counts have remained normal during this period without evidence of thrombocytopenia or anemia. Another surgical biopsy of the sternum in March, 1952, showed myelosclerosis without significant change. The spleen was noted to be considerably smaller. The dose of cortisone has been reduced to 75 mg. per day and the patient has continued to feel extremely well during the twelve months since therapy was instituted.

Comment: This patient has myelosclerosis with myeloid metaplasia and has responded well to cortisone. Although anemia was not severe, reticulocytosis developed and the platelet count rose from thrombocytopenic levels to normal. This case may represent a secondary rather than primary bone marrow failure because of a history of exposure to benzene. In either circumstance the administration of cortisone has been followed by striking clinical and hematologic improvement.

"*Refractory*" *Anemia with Normally Cellular Marrow*

The following six patients all had anemias characterized by failure of red cell production in spite of normally cellular bone marrow without morphologic abnormality of the erythroid elements.

Case V. H. B. (B. H. No. 174056) had always enjoyed excellent health until 1949 when, at age fifty-seven, she consulted a physician because of easy fatigability and weakness of one year's duration. (Fig. 6.) Slight macrocytic anemia was noted and bone marrow examination was reported to be normally cellular. Iron and liver were given without effect and a diagnosis of refractory anemia was made. The patient was treated with blood transfusions, receiving 500 cc. approximately every two weeks. When she was first seen at Barnes Hospital in January, 1951, a total of forty-four transfusions had been received. Examination at this time was essentially within normal limits except for moderate pallor. The spleen was not palpable. Laboratory data revealed a red blood count of 2,770,000 per cu. mm. with 9.0 gm. of hemoglobin per 100 cc. Platelet and white blood counts were normal and the blood film

showed moderate anisocytosis and poikilocytosis. Reticulocytes were 0.2 per cent. The bone marrow was normally cellular without abnormality except for an increase in the number of normoblasts and occasional multinucleated red cells. Ashby survival studies revealed a bilinogen excretion was 343 mg. per day with a hemolytic index of 32. The Coombs test was negative. Seven blood transfusions were given over a two-week period and splenectomy was done on July 20, 1951. The spleen (325 gm.) showed evidence of fibrosis and hemosiderosis.

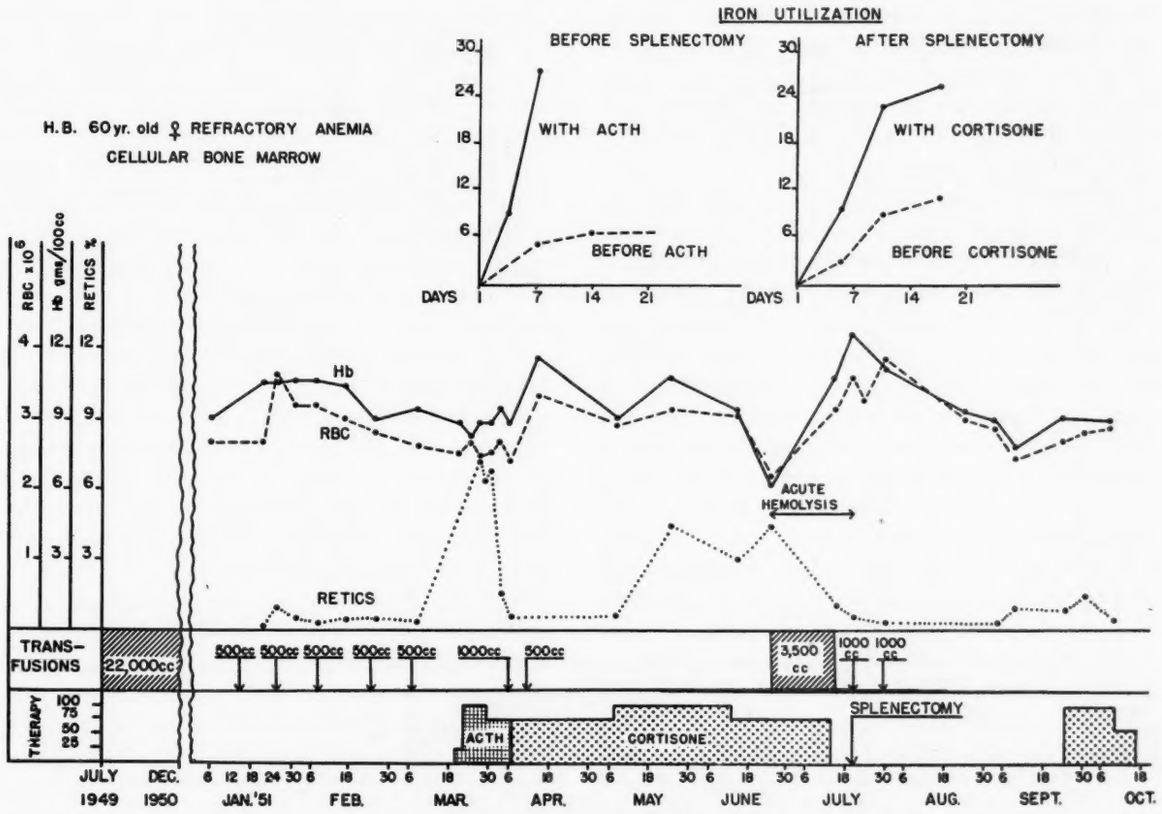


FIG. 6. Case v. Hematologic observations from July, 1949 to October, 1951.

normal life span for transfused erythrocytes. Radioactive iron studies showed 6 per cent utilization in fourteen days. The patient required one transfusion every two weeks for maintenance of comfortable red cell and hemoglobin levels. On March 21st ACTH therapy was instituted and continued until April 7th, at which time cortisone was substituted. During the administration of ACTH a reticulocytosis of 8 per cent developed and a second iron study showed 28 per cent utilization in eight days. Cortisone was continued for approximately three months, during which time the patient felt considerably better; the red cell and hemoglobin levels remained relatively constant without further transfusions. However, during the latter part of June, 1951, evidence of hemolysis developed rather suddenly, with a rapid fall in the peripheral blood values. The fecal urobilinogen excretion was 343 mg. per day with a hemolytic index of 32. The Coombs test was negative. Seven blood transfusions were given over a two-week period and splenectomy was done on July 20, 1951. The spleen (325 gm.) showed evidence of fibrosis and hemosiderosis. The patient was given 1,000 cc. of blood on July 29th. The average life span of the transfused cells was determined to be 110 days. Following splenectomy the fecal urobilinogen excretion decreased to 100 mg. per day. During August and September no further transfusions were given but the red cell and hemoglobin levels fell slowly. In nineteen days 11 per cent of an injected dose of radioactive iron was utilized. Cortisone was started on September 25th and continued until October 16th, when therapy had to be stopped because of edema and hypertension. During this period there was a slight rise in the patient's red count and the radioiron utilization increased to 26 per cent in seventeen days. After the cortisone was discontinued the red cell count again fell slowly and six transfusions were required during the next four months. In April, 1952, broncho-

pneumonia and acute hepatitis developed and the patient expired on April 30th at another hospital. Permission for autopsy was not obtained.

Comment: This patient's anemia was characterized by lack of adequate red blood cell production in spite of normally cellular marrow. The administration of ACTH and cortisone resulted in increased erythropoietic activity and a decreased transfusion requirement. An acute hemolytic episode developed during the course of her illness; this was completely alleviated by splenectomy. Subsequently the patient continued to show evidence of decreased red blood cell production although it was less severe following the operation. The response to cortisone was considered moderate and there was only partial improvement in red cell production after removal of the spleen. Death was due to acute hepatitis, which was presumably related to the numerous transfusions.

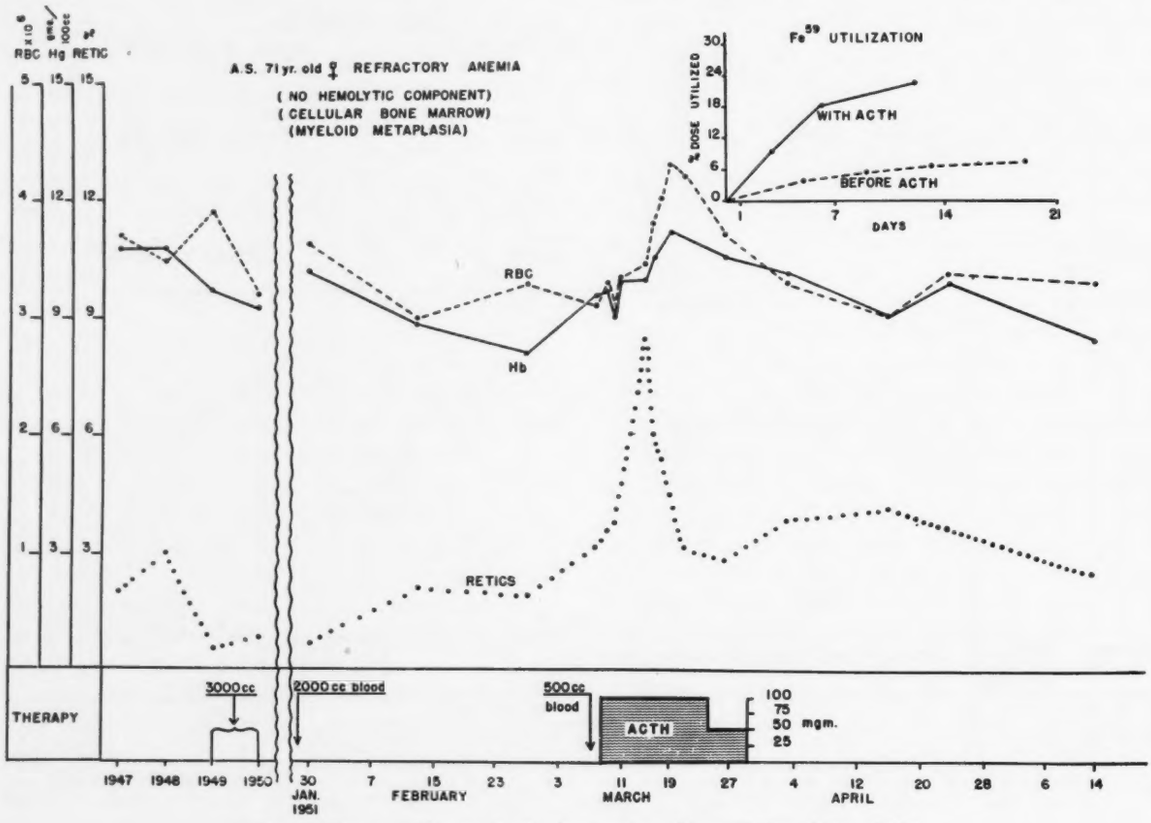


FIG. 7. Case VI. Hematologic observations from 1947 to May, 1951.

CASE VI. A. S. (B. H. No. 155808) was first seen in 1947 at age sixty-seven, with symptoms of fatigue and moderate pallor of several months' duration. (Fig. 7.) Physical examination revealed an elderly well developed woman, with marked splenomegaly. Laboratory data showed a red cell count of 3,700,000 per cu. mm., hemoglobin 10.6 gm. per 100 cc., reticulocytes 2.2 per cent, white blood count 8,600, and platelet count approximately 1,000,000. Marked variation in the size and shape of the erythrocytes was noticed on the blood film; moderate numbers of immature white cells and nucleated red cells were seen. Bone marrow was normally cellular with increased numbers of normoblasts; the myeloid cells did not appear abnormal and the megakaryocytes were increased. No history of exposure to toxic substances could be obtained. The clinical impression was refractory anemia with myeloid metaplasia. The patient got along satisfactorily until the latter part of 1949 at which time the anemia became somewhat more severe and she was given her first blood transfusion. During the next twelve months she received 3,000 cc. of blood. Examination in January, 1951, revealed splenomegaly extending to the pelvic brim, a red cell count of 2,500,000 with 6.3 gm. per cent hemoglobin, and 8,000 white blood cells per cu. mm.

A splenic biopsy showed evidence of myeloid metaplasia. Transfused cells, followed by the technic of differential agglutination, disappeared from the peripheral blood in approximately ninety days. The Coombs test was negative. Radioactive iron studies revealed 6 per cent utilization in fourteen days. Additional blood transfusions were given and during March, 1951, ACTH was administered for a period of sixteen days. A reticulocytosis of 9 per cent developed and there was a slight increase in the red cell count. Radioactive iron studies repeated during the course of ACTH revealed 23 per cent utilization in twelve days. During the latter part of 1951 progressive symptoms of weakness, increased fatigability and dyspnea on exertion developed. By November, 1951, it was observed that the transfusion requirement had increased considerably and a repeat Ashby survival study showed a life span for normal erythrocytes of approximately fifty days. Fecal urobilinogen excretion was 299 mg. per day with a hemolytic index of 57. Because of this evidence that red cells were being destroyed at an accelerated rate, splenectomy was performed on January 13, 1952. The spleen weighed 1,660 gm. and microscopic examination revealed extensive extramedullary hematopoiesis, hemosiderosis and chronic passive congestion. Several infarcts were noted. Following the operation evidence of intracerebral thrombosis developed and the patient's platelet count was 3,500,000. In spite of supportive therapy and anticoagulant control she expired on January 21, 1952. Postmortem examination showed moderate myeloid and megakaryocytic hyperplasia of the bone marrow, recent thrombi in the portal vein, small vessels of the lungs, brain and wall of the ileum and colon, and hemorrhage into the peripancreatic retroperitoneal space.

Comment: The bone marrow failure in this individual corresponded in some respects to the clinical description of agnogenic myeloid metaplasia as reported by Jackson, Parker and Lemon.[33] The administration of ACTH was followed by a reticulocyte response and increased iron utilization for hemoglobin synthesis; however anemia was not a severe factor in her disease until late in the course, when hemolysis became manifest. Splenectomy was done for this reason but the patient succumbed to cerebral thrombosis shortly thereafter, presumably due to the striking postoperative thrombocytosis. Block and Jacobson[34] have discussed the clinical characteristics of myeloid metaplasia and Claman and Collier[35] reported a case of acute hemolytic anemia complicating myeloid metaplasia of the spleen, treated by splenectomy.

Case VII. F. L. (B. H. No. 198040) was sixty-two years of age when he was first seen by his physician in 1949. He gave a history of weakness and easy fatigability of about six months' duration. Examination revealed essentially normal physical status without any significant past history of illness or exposure to toxic agents. A slightly macrocytic, normochromic anemia was found and bone marrow aspiration was interpreted as showing normal cellularity without abnormal cell type. A diagnosis of refractory anemia was made and the patient was treated with iron and liver without benefit. He was treated with blood transfusions for two years, beginning in July, 1949. During this interval he received a total of sixty-five transfusions of 500 cc. each; these were given when necessary in order to maintain a comfortable red cell level of around 3,500,000. In the early part of 1951 a gray-brown pigmentation of the skin was noted and enlargement of the liver was observed. The spleen was not palpable and the bone marrow remained cellular. Reticulocyte counts were consistently below 1 per cent. When first seen at Barnes Hospital in April, 1951, the following additional laboratory data were obtained: the serum iron-binding protein was completely saturated at a level of 300 μg. per cent; an Ashby survival study indicated a life span of approximately 100 days when normal erythrocytes were transfused into the patient; fecal urobilinogen excretion was 151 mg. per day with a hemolytic index of 12; and a radioactive iron study showed 1.2 per cent utilization after twenty days. (Fig. 8.) When a second intravenous dose of radioiron was given during the administration of ACTH and cortisone, 11.9 per cent appeared as newly synthesized hemoglobin in fifteen days. On July 18, 1951, the patient's spleen was removed. The organ weighed 220 gm.; there was evidence of extensive hemosiderosis and chronic passive congestion. Following the operation the patient did well, requiring no further transfusions for over two months. From October on, however, his counts began to fall slowly and one transfusion was given approximately every five weeks in order to relieve symptoms of weakness and to keep the red cell count above 3,500,000.

However, cardiac decompensation became a major problem in management and despite all measures to combat heart failure, he expired on June 21, 1952, with evidence of generalized edema and decompensation. A radioactive iron study carried out shortly after the splenectomy and a decreased need for transfusions. Splenectomy also resulted in a lowered transfusion requirement but the response was not striking.

CASE VIII. R. C. (B. H. No. 129568), a sixty-four year old white man, was first noted to have a moderate macrocytic anemia in 1945 when

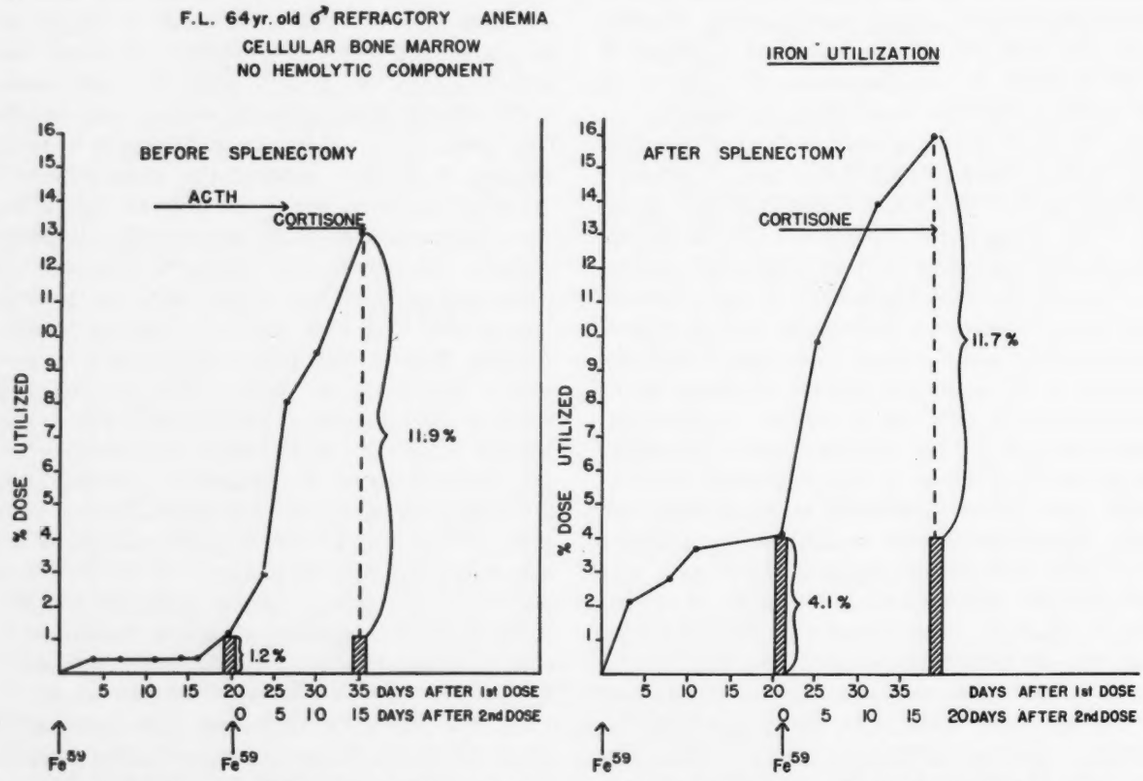


FIG. 8. Comparison of utilization of radioiron for hemoglobin synthesis in Case VII with and without cortisone therapy and before and after splenectomy.

revealed 4.1 per cent utilization in twenty days and a similar study repeated during a short course of cortisone indicated 11.6 per cent utilization in sixteen days. Autopsy findings included hypertrophy and dilatation of the heart and markedly increased iron deposition in the skin, liver, heart, pancreas, adrenal, thyroid and lymph nodes. Fibrosis of the liver and pancreas were also demonstrated. The bone marrow appeared cellular with diffuse hemosiderin deposition.

Comment: This patient illustrates well the serious complications that are likely to develop following numerous transfusions.[36] Undoubtedly the extensive hemosiderosis contributed to the myocardial failure. Despite a normally cellular marrow the erythropoietic capacity was very low. ACTH and cortisone evoked a moderate response with a slight increase in iron utilization

he was admitted to the hospital for treatment of erysipelas; his physician assumed that the anemia was secondary to the infection. Red cell count was 3,130,000 per cu. mm., hemoglobin 12.2 gm. per cent, and white count normal. The patient remained asymptomatic until the middle of 1951 when he began to feel abnormally tired and noticed pallor. Laboratory studies, the first since 1945, revealed a moderate anemia of 2,580,000 red cells, 10.9 gm. of hemoglobin per 100 cc., reticulocytes 1.8 per cent, platelets 690,000, white cells 7,650 with a normal differential. Bone marrow aspiration indicated a cellular marrow with normal myeloid and megakaryocytic elements, an increase in the number of nucleated red cells, and a moderate increase in young erythroblasts. The patient failed to respond to administration of folic acid, folinic acid and vitamin B_{12}; a diagnosis of

refractory macrocytic anemia was made. Physical examination was within normal limits and careful clinical study revealed no primary cause to which the anemia could be ascribed. Hepatic function tests, serum N.P.N., and a basal metabolism test were within normal limits. for two weeks. During this time there was an increase in iron utilization to 56 per cent in fourteen days. He has continued to have a moderate macrocytic anemia but is free of symptoms except for fatigue and has required only occasional transfusions.

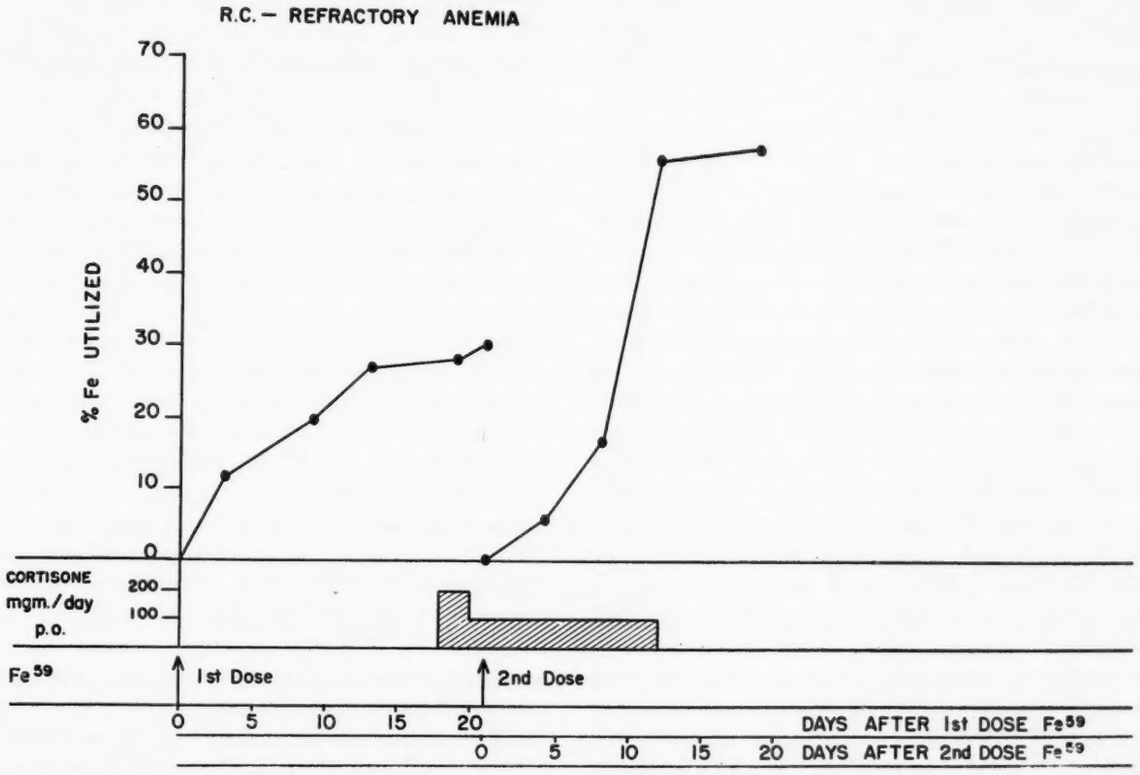


FIG. 9. Comparison of utilization of radioiron for hemoglobin synthesis in Case VIII before and during the administration of cortisone.

Upon re-evaluation of the patient in August, 1951, the following data were obtained: red cell counts varied between 2,270,000 and 3,340,000 without transfusions; the hemoglobin values ranged between 10.4 and 11.6 gm. per cent. Reticulocytes remained around 0.5 per cent with a normal white count, platelet count and differential. The Coombs test was negative and bone marrow examination again showed moderate hyperplasia of the erythroid elements. Serum iron determinations on two occasions were 368 and 354 μg. per cent with complete saturation of the iron-binding protein. The fecal urobilinogen excretion was 410 mg. per day with a hemolytic index of 62. The determination of the survival time of transfused erythrocytes showed a life span of eighty to ninety days. An intravenous radioactive iron study revealed 27 per cent utilization in fourteen days. (Fig. 9.) The patient was given 100 mg. of cortisone daily by mouth

Comment: The erythropoietic effect of cortisone in this patient was demonstrated by an increased iron utilization. There is evidence of increased red cell destruction as well as decreased production. The anemia resulting from the disordered balance of the erythropoietic equilibrium, however, has not been severe enough to justify the consideration of splenectomy.

CASE IX. J. C. is a physician fifty-seven years of age in whom excessive fatigue and increasing pallor developed in 1950. There was no past history of significant disease and physical examination was within normal limits. Laboratory data revealed a red cell count of 3,400,000 with 10.4 gm. of hemoglobin per 100 cc., white count 5,850 with a normal differential, platelets 1,000,000 and reticulocytes 1.7 per cent. Aspirated bone marrow appeared normally cellular without evidence of abnormality in the erythroid or myeloid series. A diagnosis of

refractory anemia was made and in October, 1950, he received the first of numerous blood transfusions. A surgical biopsy of the sternum was interpreted as showing generalized hyperplasia without morphologic alteration of the erythroid or myeloid elements. From April, 1951, until December of that year he received a total of 6,500 cc. of whole blood, averaging approximately one 500 cc. transfusion every three weeks. An Ashby survival study done in December, 1951, demonstrated a life span of approximately seventy days for transfused normal erythrocytes and radioactive iron studies showed 11 per cent utilization after twenty-nine days. The patient was then given 100 mg. of cortisone per day by mouth and a repeat radioiron determination revealed 29 per cent of the injected dose in the circulating hemoglobin after sixteen days. Cortisone was started on January 2, 1952, and continued until May, 1952. During this time the need for transfusions decreased considerably although in March and April, when the cortisone dose was decreased to 50 mg. per day, the transfusion requirement again increased. Five transfusions were given over the period of cortisone administration. At the present time the patient feels quite well although frequent transfusions are necessary in order to maintain a comfortable red cell level.

Comment: In spite of a cellular marrow this patient requires numerous transfusions in order to maintain a comfortable red blood cell level. The administration of cortisone was accompanied by both objective and subjective evidence of increased erythropoiesis; although the over-all transfusion requirement was not strikingly improved, it was noted that during periods of increased dosage (100 mg. daily) the need for blood transfusions was greatly decreased.

Case x. M. S. (B. H. No. 199907), a sixty year old white woman, was first seen in 1951 with a history of easy fatigability during the previous year and sporadic episodes of spontaneous purpura and ecchymoses. Four years before admission to the hospital her physician had found her to be anemic and had treated her with liver and iron, without benefit. There was no history of any other significant illness. Physical examination revealed the patient to be pale, with several ecchymoses scattered over the body. The liver and spleen were not palpable and there were no other significant physical findings. Laboratory data showed a red count of 2,290,000 per cu. mm., hemoglobin 7.7 gm. per 100 cc., reticulocytes 3.2 per cent, platelets 32,000, white count 2,000 with 40 per cent segmented neutrophils, 4 per cent band forms, 50 per cent lymphocytes and 2 per cent monocytes. Bone marrow aspiration revealed normally cellular marrow with moderate stimulation of erythroid elements. There was no evidence of cellular immaturity. The patient was considered to have pancytopenia due to refractory anemia. Further studies showed a basal metabolism rate of −20 per cent. She was treated with thyroid extract for eight weeks without hematologic change, although the basal metabolism rate rose to −4 per cent. Fecal urobilinogen excretion was within normal limits and an Ashby survival time of normal red cells transfused into the patient was approximately 120 days. The Coombs test was negative and a radioactive iron study showed 61 per cent utilization in fifteen days. In November, 1951, the patient was given daily intravenous injections of 20 mg. of ACTH; the reticulocytes rose to 10 per cent and the white count returned to normal. A radioactive iron study repeated while ACTH was being given showed 100 per cent utilization in nine days. The pancytopenia recurred when ACTH was discontinued. On January 28, 1952, the spleen was removed. It weighed 80 gm. and showed evidence of lymphoid hyperplasia and chronic passive congestion. Following the operation there was no immediate change in the platelet level but the red cell and hemoglobin values persisted within normal limits and the white count varied between 5,000 and 8,000 with a normal differential. When last seen in January, 1953, the patient was free of symptoms; laboratory studies showed 12.5 gm. of hemoglobin per 100 cc., 3,500,000 red cells per cu. mm., 3.4 per cent reticulocytes, 5,600 white cells and 100,000 platelets.

Comment: This patient presented evidence of a cellular bone marrow with peripheral pancytopenia. It is difficult to determine whether this condition represents splenic panhematopenia[37] or refractory anemia with bone marrow failure. The administration of ACTH resulted in return of the peripheral blood values to normal; they reverted to the previous low levels when therapy was stopped. Radioactive iron utilization was strikingly increased while she received ACTH. Splenectomy has resulted in restoration of the patient's peripheral blood values to approximately normal levels and she has been free of symptoms for the year following operation.

REMARKS

The data presented for these ten patients demonstrate the way in which one may evaluate the erythropoietic equilibrium in patients with bone marrow failure. The rate of red cell production was subnormal, as would be expected, but the rate of red cell destruction was also accelerated in six of the patients. (Table I.) Administration of cortisone or ACTH to nine of the subjects stimulated erythrocytogenesis in all instances; the effect was only slight, however, in patients H. B. and F. L. (Cases V and VII, respectively.) Splenectomy was performed in seven patients, including four of those with increased hemolysis. One of the latter died during the immediate postoperative period. In the remaining three the rate of red cell destruction returned to normal or near normal. Red cell production was increased slightly in two, and enough to return the red cell count to normal in three; in the sixth splenectomized patient (G. R., Case III) erythrocytogenesis has not been evaluated after splenectomy and the red cell equilibrium established at about three and a half million cells may have resulted solely because the hemolytic component was removed. Splenectomy has not been done in the remaining three patients for the following reasons: (1) R. C. (Case VIII) is an elderly gentleman with only minimal symptoms from his anemia and with evidences of moderately severe coronary artery disease; (2) J. C. (Case IX) is a physician who has elected to postpone the operation; (3) O. D. (Case IV) tolerates maintenance doses of cortisone well, and is so free of symptoms that operation has not seemed advisable.

In these ten patients, therefore, striking clinical improvement resulted from splenectomy in four instances and from continuous cortisone

TABLE I

SUMMARY OF HEMATOLOGIC OBSERVATIONS ON TEN PATIENTS WITH CHRONIC BONE MARROW FAILURE

Case No. and Patient	Before Treatment				Type of Therapy	With Treatment			
	Bone Marrow	Hemolytic Component	Red Cell Production	Transfusions		Bone Marrow	Hemolytic Component	Red Cell Production	Transfusions
I, E. H.	Erythroid hypoplasia	Yes	Decreased	Frequent	ACTH	Normal	... *	Improved	None
					Splenectomy	Normal	No	Improved	Infrequent
					Cortisone	Normal	No	Improved	None
II, L. H.	Erythroid hypoplasia	No	Decreased	Frequent	Splenectomy	Normal	No	Improved	None
III, G. R.	Myelosclerosis	Yes	Decreased	Frequent	Cortisone	.....	Yes	Improved	Less frequent
					Splenectomy	.....	No	Improved	None
IV, O. D.	Myelosclerosis	No	.....	Infrequent	Cortisone	.....	...	Improved	None
V, H. B.	Normal	No	Decreased	Frequent	ACTH/cortisone	Normal	No	Slightly improved	Infrequent
		Yes	Decreased	Frequent	Splenectomy	Normal	No	Slightly improved	Infrequent
VI, A. S.	Normal (myeloid metaplasia)	No	Decreased	Infrequent	ACTH	Normal	No	Improved	Infrequent
		Yes	Decreased	Frequent	Splenectomy	(Patient died postoperatively)			
VII, F. L.	Normal	No	Decreased	Frequent	ACTH/cortisone	Normal	No	Slightly improved	Infrequent
					Splenectomy	Normal	No	Slightly improved	Infrequent
VIII, R. C.	Normal	Yes	Decreased	None	Cortisone	Normal	...	Improved	None
IX, J. C.	Normal	Yes	Decreased	Frequent	Cortisone	Normal	...	Improved	Infrequent
X, M. S.	Normal	No	Decreased	None	ACTH	Normal	No	Improved	None
					Splenectomy	Normal	No	Improved	None

* Not determined

administration in one. Two patients were only slightly improved by splenectomy, one died during the immediate postoperative period, and two are being treated conservatively. The dramatic character of the five beneficial results can be appreciated only when considered against the background of subnormal activities and frequent transfusions which otherwise would have continued. It is emphasized again, however, that splenectomy was performed only after careful evaluation of the erythropoietic equilibrium in these patients had demonstrated: (1) an increased rate of red cell production following cortisone or ACTH administration; and (2) in some instances, a hemolytic component to the anemia.

Use of the utilization of injected radioiron for hemoglobin synthesis as a measure of erythrocytogenesis deserves special comment. Finch and co-workers[14] have demonstrated that other factors such as the state of the iron stores may influence radioiron utilization. However, in the cases herein reported all determinations were repeated before and during attempts to influence red blood cell production without significant change in the level of iron stores; consequently each case served as its own control. Any variation in iron utilization under these conditions can be interpreted as reflecting a change in erythropoietic functional activity. Serum iron levels were uniformly high and the plasma iron-binding protein was saturated; no significant changes in these values were noted during the administration of ACTH or cortisone.

Recent studies have employed measurement of the plasma iron clearance rate as an index of erythropoietic function.[15,38–40] This technic promises to be very helpful since, when combined with the measurement of iron utilization for hemoglobin synthesis, it permits calculation of absolute amounts of hemoglobin synthesized and delivered to the peripheral blood per day. Unfortunately the radioactive iron of very high specific activity required for the technic has not, until recently, been available in this laboratory. However, the data obtained in this investigation were used to determine only whether or not erythropoietic function could be influenced favorably by the various therapeutic measures. For measuring changes in the rate of erythropoiesis the radioiron utilization technic is satisfactory.

The anemia in all ten patients was characterized by a decrease in bone marrow function as indicated by reticulocytopenia and a lowered iron utilization. No correlation between the morphologic appearance of the bone marrow and the erythropoietic functional status could be made. In six of the patients studied there was evidence of a hemolytic component to the anemia, as detected by the methods outlined. When present, the severity of hemolysis seemed to be related to the duration of the bone marrow failure, the size of the spleen and the number of transfusions previously administered. Hemosiderosis was invariably noted when extensive transfusion therapy had been administered over a long period of time. In no case was an autoagglutinin demonstrated by the Coombs technic.[41]

Although few specific data on the effect of adrenocorticotrophic hormone or cortisone on bone marrow function or iron utilization are available, attention has been called to the effect of these substances on hematopoiesis in general[42,43] and on iron metabolism specifically.[44] Daughaday and associates[45] have discussed the effect of various endocrinopathies on the blood and concluded that regulation of blood formation is not primarily under hormonal control. Gordon and associates[46] have reported that the anemia resulting from adrenalectomy in rats can be corrected with the administration of cortisone, and Garcia[47] has produced polycythemia in normal rats after prolonged administration of ACTH. Selye[48] has been able to produce myeloid transformation of fat cells by the administration of a crude anterior pituitary extract. Only a few clinical reports of the specific use of adrenal hormone therapy in bone marrow failure are available.[22,49–51] The data in the present report derived from those patients who received such treatment indicate that a favorable influence on bone marrow function may not always be detectable by brief clinical observation but may be demonstrated by such indirect measurement as the efficiency of iron utilization. With this technic it was possible to detect a significant latent potentiality to produce more red blood cells in five of the seven patients studied. In those cases in which ACTH and/or cortisone exerted a favorable effect, as shown by an increased iron utilization for hemoglobin synthesis, there frequently was evidence of reticulocytosis and a decrease in transfusion requirement.

Isolated reports of a favorable effect of splenectomy in bone marrow failure are recorded in the literature.[3,24,26–28,30,31,52,53] The

rationale for the use of splenectomy in the present cases was based upon two premises. If a hemolytic component to the anemia was demonstrable, it seemed likely that the accelerated destruction of erythrocytes might be due to increased phagocytosis, sequestration and stasis in a spleen which had become pathologically altered as a consequence of the transfusion-induced hemosiderosis or enlarged because of extramedullary hematopoiesis. With complete failure of erythropoietic function it is theoretically possible to maintain a relatively constant red cell count with one 500 cc. transfusion every seven to ten days. This calculation is based on the fact that a normal adult destroys approximately 0.8 per cent of his circulating erythrocytes daily. If a patient requires considerably more transfusions in order to maintain a comfortable red cell value, it may be assumed that increased blood destruction is present and, therefore, removal of the factor responsible for the hemolysis should result in a decreased transfusion requirement.

The second premise upon which the rationale for splenectomy rested was the postulation that there might be a splenic inhibition of bone marrow function. Those individuals in whom an increased capacity for erythropoiesis could be demonstrated by observing a favorable influence upon iron utilization during the administration of ACTH or cortisone were uniformly benefited by splenectomy. The fact that increased erythropoietic activity was detected in some patients following removal of the spleen suggests that this organ may actually inhibit red blood cell production in certain cases of chronic primary bone marrow failure. One can only speculate upon the interrelationship of the spleen, adrenal cortex and bone marrow. If it is postulated that there is a circulating substance (hormone?) in the blood which normally promotes erythropoiesis in the bone marrow, then it is conceivable that in chronic primary bone marrow failure the spleen may directly destroy this substance or may secrete an inhibitor. Such a theory has been advocated by Johansen.[54] Conclusive experimental data are not available to arrive at a satisfactory explanation. From the clinical observations made on the ten patients in this report it is tempting to postulate that those individuals with chronic primary bone marrow failure who can be shown to respond favorably to the administration of ACTH or cortisone will be benefited by splenectomy. However, it is only through the application of physiologic technics in the evaluation of such cases that adequate criteria may be derived for the selection of patients who are likely to improve with this therapeutic approach.

SUMMARY

1. Physiologic technics are available which permit evaluation of the relative importance of inadequate production and increased destruction of red blood cells in the pathogenesis of a given anemia.

2. Data derived from these technics have been applied to the clinical management of ten patients with chronic bone marrow failure.

3. The anemia of chronic bone marrow failure is due to decreased production of red blood cells and may be associated with a hemolytic component.

4. Erythropoiesis in some patients may be stimulated by the administration of adrenocorticotrophic hormone or cortisone. Evidence is presented to suggest that it is these patients who are most likely to respond favorably to splenectomy. If a hemolytic component is also present, splenectomy tends to correct the abnormal red cell destruction.

5. The anemia of chronic bone marrow failure should not be considered entirely refractory to therapy.

Acknowledgment: The authors are indebted to the Armour Laboratories, Chicago, Ill., for the ACTH used in this study and to Merck and Co., Inc., Rahway, N. J. for generous supplies of cortisone.

Addendum: Since this manuscript was submitted a third patient with myelosclerosis has been studied for a sufficient period of time to warrant inclusion in this series. A. G. (B. H. No. 208589) was forty years old when enlargement of the spleen was noted in 1940. The peripheral blood values remained normal until November, 1951, when a moderate normocytic normochromic anemia developed. In April, 1952, this became more severe and was associated with thrombocytopenia. Studies at that time revealed a decreased radioiron utilization, immature white cells and red cells in the peripheral blood and a bone marrow biopsy was interpreted as myelosclerosis. Frequent transfusions became necessary for maintenance of hemoglobin levels and in May, 1952, she started taking cortisone. During treatment the reticulocyte level rose to

11 per cent, the transfusion requirement decreased and the radioiron utilization increased. However, in August, 1952, it became obvious that hemolysis contributed significantly to the anemia. This was demonstrated by a shortened Ashby survival study and an increased hemolytic index. On August 29, 1952, a 1,700 gm. spleen was removed. Pathologic examination revealed myeloid metaplasia and extensive hemosiderosis. Subsequent to the operation, the reticulocytes rose to a maximum of 20 per cent and the red count, white count and platelet count returned to normal without further transfusions or cortisone therapy. When last seen in January, 1953, she was entirely asymptomatic.

A recent article by Green and associates reviews the literature on splenectomy in myeloid metaplasia and presents data on five additional cases.[55]

REFERENCES

1. Ehrlich, P. Über einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarks. *Charité-Ann.*, 13: 300, 1888.
2. Boon, T. H. and Walton, J. N. Aplastic anemia. *Quart. J. Med.*, 20: 75, 1951.
3. Wintrobe, M. M. Clinical Hematology, 3rd ed. Philadelphia, 1951. Lea and Febiger.
4. Rhoads, C. P. and Miller, D. K. Histology of the bone marrow in aplastic anemia. *Arch. Path.*, 26: 648, 1938.
5. Bomford, R. R. and Rhoads, C. P. Refractory anemia. *Quart. J. Med.*, 10: 175, 1941.
6. Vaquez, M. H. and Aubertin, C. L'anémie pernicieuse d'apres les conceptions actuelles. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 21: 288, 1904.
7. Frank, E. Aleukia haemorrhagica. Aplastische (aregenerative) Anämie-Panmyelophthisie. *Berl. klin. Wchnschr.*, 52: 961, 1915.
8. Lescher, F. G. and Hubble, D. A correlation of certain blood diseases on the hypothesis of bone marrow deficiency or hypoplasia. *Quart. J. Med.*, 1: 425, 1932.
9. Thompson, W. P., Richter, M. N. and Edsall, K. S. An analysis of so-called aplastic anemia. *Am. J. M. Sc.*, 187: 77, 1934.
10. Middleton, W. S. and Meyer, O. O. Marrow insufficiency. *Ann. Int. Med.*, 8: 1575, 1935.
11. Vaughan, S. L. Aplastic anemia. *New York State J. Med.*, 42: 978, 1942.
12. Wyatt, J. P. and Sommers, S. C. Chronic marrow failure, myelosclerosis, and extramedullary hematopoiesis. *Blood*, 5: 329, 1950.
13. Dubach, R., Moore, C. V. and Minnich, V. Studies in iron transportation and metabolism. v. Utilization of intravenously injected radioactive iron for hemoglobin synthesis, and an evaluation of the radioactive iron method for studying iron absorption. *J. Lab. & Clin. Med.*, 31: 1201, 1946.
14. Finch, C. A., Gibson, J. G., Peacock, W. C. and Fluharty, R. G. Iron metabolism. Utilization of intravenous radioactive iron. *Blood*, 4: 905, 1949.
15. Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M. and Laurence, J. H. Plasma and red cell iron turnover in normal subjects and in patients having various hematopoietic disorders. *J. Cl.n. Investigation*, 29: 1041, 1950.
16. Dameshek, W. A method for the simultaneous enumeration of blood platelets and reticulocytes. *Arch. Int. Med.*, 50: 579, 1932.
17. Schwartz, S., Sborov, V. and Watson, C. J. Studies of urobilinogen. iv. The quantitative determination of urobilinogen by means of the Evelyn photoelectric colorimeter. *Am. J. Clin. Path.*, 14: 598, 1944.
18. Miller, E. B., Singer, K. and Dameshek, W. Use of the daily fecal output of urobilinogen and the hemolytic index in the measurement of hemolysis. *Arch. Int. Med.*, 70: 722, 1942.
19. Dacie, J. V. and Mollison, P. L. Survival of normal erythrocytes after transfusion to patients with familial hemolytic anemia. *Lancet*, 1: 550, 1943.
20. Moore, C. V., Minnich, V. and Welch, J. Studies in iron transportation and metabolism. iii. The normal fluctuations of serum and "easily split-off" blood iron in individual subjects. *J. Clin. Investigation*, 18: 543, 1939.
21. Rath, C. E. and Finch, C. A. Chemical, clinical and immunological studies of the products of human plasma fractionation. xxxviii. Serum iron transport. Measurement of iron-binding capacity of serum in man. *J. Clin. Investigation*, 28: 79, 1949.
22. Loeb, V. In discussion on Hill, F. M. and Hunter, R. B.[49]
23. Kark, R. M. Two cases of aplastic anemia. *Guy's Hosp. Rep.*, 87: 343, 1937.
24. Palmén, K. and Vahlquist, B. Stationary hypoplastic anemia. *Acta haemat.*, 4: 273, 1950.
25. Cathie, I. A. B. Erythrogenesis imperfecta. *Arch. Dis. Childhood*, 25: 313, 1950.
26. Whitby, L. E. H. and Britton, C. J. C. Disorders of the Blood, 6th ed. Philadelphia, 1950. The Blakiston Co.
27. Estren, S. and Dameshek, W. Familial hypoplastic anemia of childhood. *Am. J. Dis. Child.*, 73: 671, 1947.
28. Dacie, J. V. and Gilpin, A. Refractory anemia (Fanconi type). *Arch. Dis. Childhood*, 19: 155, 1944.
29. Donhauser, J. L. The human spleen as a hematoplastic organ, as exemplified in a case of splenomegaly with sclerosis of the bone marrow. *J. Exper. Med.*, 10: 559, 1908.
30. Andersen, T. and Sørensen, G. Osteomyelosclerosis combined with splenogenic inhibition of the bone marrow. *Acta med. Scandinav., suppl.* 266, p. 179, 1952.
31. Edwards, H. C. The practice and consequences of splenectomy. *Lancet*, 2: 601, 1951.
32. Franks, R. B. Myelofibrosis. *Proc. Roy. Soc. Med.*, 45: 30, 1952.
33. Jackson, H., Parker, F. and Lemon, H. M. Agnogenic myeloid metaplasia of the spleen. *New England J. Med.*, 222: 985, 1940.

34. Block, M. and Jacobson, L. O. Myeloid metaplasia. *J. A. M. A.*, 143: 1390, 1950.
35. Claman, M. A. and Collier, W. J. Acute hemolytic anemia associated with myeloid metaplasia of the spleen. *Arch. Int. Med.*, 89: 431, 1952.
36. Wyatt, J. P. and Goldenberg, H. Hemosiderosis in refractory anemia. *Arch. Int. Med.*, 83: 67, 1949.
37. Doan, C. A. and Wright, C. S. Primary congenital and secondary acquired splenic panhematopenia. *Blood*, 1: 10, 1946.
38. Wasserman, L. R., Rashkoff, I. A., Leavitt, D., Mayer, J. and Port, S. The rate of removal of radioactive iron from the plasma—an index of erythropoiesis. *J. Clin. Investigation*, 31: 32, 1952.
39. Huff, R. L., Tobias, C. A. and Lawrence, J. H. A test for red cell production. *Acta haemat.*, 7: 129, 1952.
40. Finch, S. C. and Ross, J. F. Significance of plasma iron turnover rate. *Federation Proc.*, 11: 414, 1952.
41. Coombs, R. R. A., Mourant, A. E. and Race, R. R. A new test for the detection of weak and "incomplete" Rh agglutinins. *Brit. J. Exper. Path.*, 26: 255, 1945.
42. Wintrobe, M. M. ACTH and cortisone in hemopoietic disorders. *Am. J. Med.*, 9: 715, 1950.
43. Dameshek, W. ACTH and its hematologic impact. *Blood*, 5: 779, 1950.
44. Hamilton, L. D., Gubler, C. J., Ashenbrucker, H., Cartwright, G. E. and Wintrobe, M. M. Studies on the relationship of the adrenal cortex to the experimental production of hypoferremia in rats. *Endocrinology*, 48: 44, 1951.
45. Daughaday, W. H., Williams, R. H. and Daland, G. A. The effect of endocrinopathies on the blood. *Blood*, 3: 1342, 1948.
46. Gordon, A. S., Piliero, S. J. and Landau, D. The relation of the adrenal to blood formation in the rat. *Endocrinology*, 49: 497, 1951.
47. Garcia, J. F. et al. Increase in circulating red cell volume of normal and hypophysectomized rats after treatment with ACTH. *Proc. Soc. Exper. Biol. & Med.*, 76: 707, 1951.
48. Selye, H. and Stone, H. Hormonally induced transformation of adrenal into myeloid tissue. *Am. J. Path.*, 26: 211, 1950.
49. Hill, J. M. and Hunter, R. B. ACTH therapy in refractory anemia, Proceedings of the Second Clinical ACTH Conference, vol. 2, p. 181. New York, 1951. The Blakiston Co.
50. Spaet, T. H., Rosenthal, M. G. and Dameshek, W. ACTH and cortisone in the treatment of the aplastic and "adynamic" anemias. *Bull. New England M. Center*, 13: 252, 1951.
51. Gasser, C. Aplastische Anämie (chronische Erythroblastophthise) und Cortison. *Schweiz. med. Wchnschr*, 81: 1241, 1951.
52. Doan, C. A. Hypersplenism. *Bull. New York Acad. Med.*, 25: 625, 1949.
53. Welch, C. S. and Dameshek, W. Splenectomy in blood dyscrasias. *New England J. Med.*, 242: 601, 1950.
54. Johansen, C. A new theory of splenic marrow inhibition. Proceedings of the Third International Congress of the International Society of Hematology, p. 108, New York, 1951. Grune and Stratton.
55. Green, T. W., Conley, C. L., Ashburn, L. L. and Peters, H. R. Splenectomy for myeloid metaplasia of the spleen. *New England J. Med.*, 248: 211, 1953.

Radioactive Iron Absorption in Siderosis (Hemochromatosis) of the Liver*

CAPT. RALPH E. PETERSON, M.C. *and* CAPT. RICHARD H. ETTINGER, M.C.

Bethesda, Maryland *Chicago, Illinois*

EXPLANATIONS for the increase of stored iron in siderosis of the liver have not been adequately supported by experimental data. Because of the large quantities of storage iron occurring in this disease and because there is no physiologic mechanism to provide for the excretion of significant amounts of iron, most investigators have quite naturally sought an explanation relating to an increased absorption of iron from the gastrointestinal tract.

Balance studies of iron absorption in normal subjects and in patients with various diseases, including hemochromatosis, have been made using non-radioactive iron salts.[1–5] In many of the more recent studies radioactive iron salts have been used.[6–13] Much of this work with both types of iron can be criticized because the amounts of iron given were far beyond the physiologic range. The balance studies with non-radioactive iron are unreliable because of the difficulty of recovering iron quantitatively from food and feces by the use of standard colorimetric procedures, and because of the many possibilities for introducing extraneous iron as a contaminant.[1] In most of the studies using radioactive iron the amount of iron incorporated into hemoglobin has been taken as the sole index of absorption.[6,10–13] Such a procedure may be valid in normal subjects and in patients with iron deficiency but is not reliable in pathologic conditions associated with increased iron storage or decreased red blood cell production.[7]

Using the balance technic we have studied the absorption of physiologic amounts of isotopic iron in five normal subjects and two patients with siderosis. One of these patients had hepatic siderosis at the time of investigation and the other was studied on two occasions after the stored iron had been removed by multiple phlebotomies.

METHODS

The iron used in these investigations was Fe^{59}, obtained from the Oak Ridge Laboratories. After twelve hours of fasting, subjects were fed 30 to 60 μg. (5 to 15 microcuries) of iron as ferric chloride in approximately 250 ml. of water. Blood was drawn one, two and three hours after administration of the iron, and the radioactivity of the iron in the serum was measured. The results of this study indicate that following oral administration of Fe^{59} the maximal concentration in the serum occurs at about two hours. Blood was also drawn at ten, fifteen and twenty days for measurement of the radioactivity of the iron in the red blood cells. Stools were collected for one to two weeks for analysis of unabsorbed iron. Over 99 per cent of the radioactive iron recoverable from stools is found in the first week; measurable amounts, however, can be detected for three to four weeks.

The radioactivity of the iron in the stools was measured by a previously described procedure which utilizes cupferron to separate inorganic ions that interfere in electroplating.[14] The serum and red blood cell radioactive iron analyses were made by the same procedure. The electroplated samples were analyzed for radioactivity with a thin mica end-window Geiger counter.

Serum iron was determined by the method of Peterson,[15] and serum iron-binding capacity by a modification of the method of Rath and Finch.[16] Liver biopsy specimens were examined and stained for iron (Prussian blue technic) by the Armed Forces Institute of Pathology. Blood

* From the Department of Biochemistry and the Department of Hepatic and Metabolic Diseases, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C.

FIG. 1. Case I. Liver biopsy section stained for iron, taken prior to initiation of phlebotomies.

volumes were arbitrarily assumed to be 70 ml. per kg. In Case I this value was confirmed by a P^{32} blood volume determination.

CLINICAL MATERIAL

CASE I. A fifty year old white male presented a history of gradual onset of fatigue and anorexia in September, 1949. One month later scleral icterus and dark urine appeared and persisted for three months. The patient was admitted to Walter Reed Army Hospital in May, 1950, complaining of fatigue, anorexia, abdominal distention and weight loss of 15 pounds. There was no history of liver or biliary tract disease prior to 1949 and no known contact with hepatotoxic agents. The dietary intake had apparently been adequate and alcohol consumption moderate.

Physical examination showed palmar erythema, spider angiomas and minimal ascites. The liver was palpated 7 cm. below the right costal margin. The hemogram, urinalysis, serum alkaline phosphatase, serum proteins and thymol turbidity were normal. Bromsulphalein retention was 20 per cent. A needle biopsy of the liver showed extensive portal fibrosis with some pseudolobulation, moderate fatty metamorphosis and pronounced siderosis of the parenchymal cells. (Fig. 1.) The serum iron was 275 μg. per cent and the serum iron-binding capacity was zero.

No hemosiderin was found in the urine or in biopsies of skin and gastric mucosa. The oral glucose tolerance test was of the characteristic "diabetic type" on two occasions. A therapeutic regimen of bed rest and high protein, high caloric diet with multiple vitamin supplements was begun. A second liver biopsy in October, 1950, was similar to the first. Sternal marrow aspiration revealed 4+ hemosiderin deposition.[17]

A program of frequent phlebotomies was begun in November, 1950. At this time the red blood cell count was 5.3 million, hemoglobin 15.0 gm. per cent and hematocrit 45 per cent. The liver was palpable 14 cm. below the right costal margin and the spleen 2 cm. below the left costal margin. Serum iron and liver function studies were unchanged. Between November, 1950, and April, 1951, the patient had eighteen phlebotomies totaling 10 L. of blood. The red

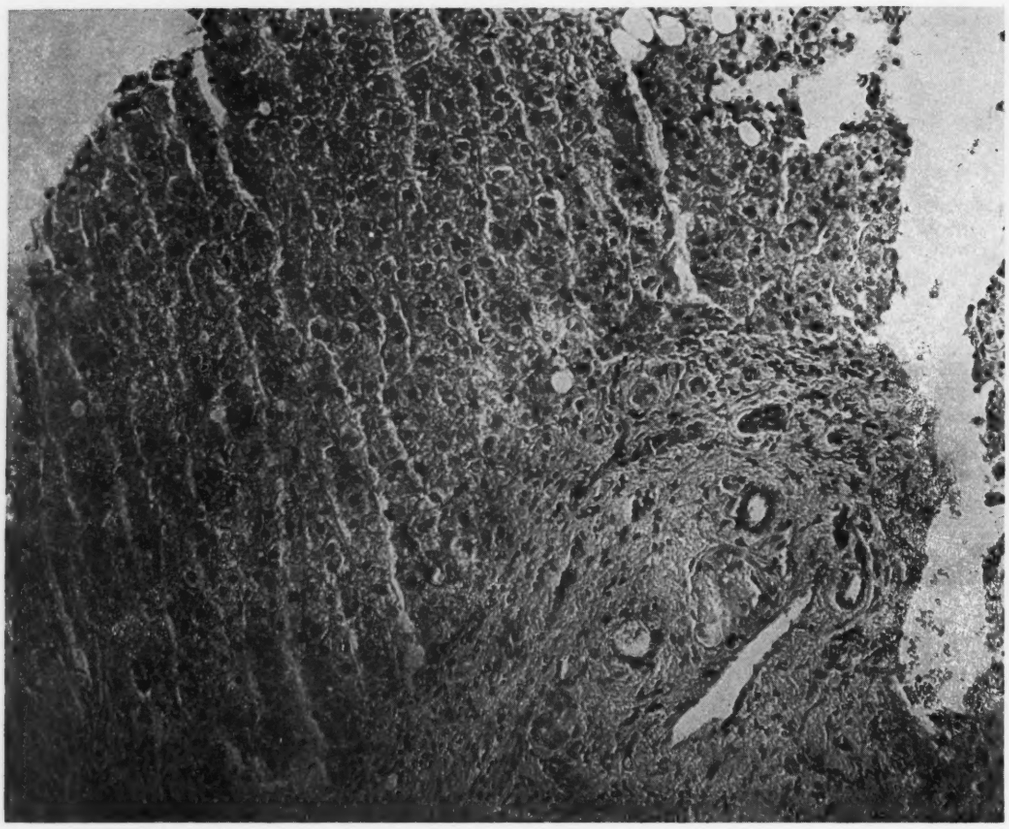


FIG. 2. Case I. Liver biopsy section stained for iron, taken after a total of 37 L. of blood was removed by phlebotomies over a period of fifteen months.

blood cell count in April, 1951, was 4.9 million, hemoglobin 14.0 gm. per cent, hematocrit 46 per cent and reticulocyte count 4.3 per cent. The patient was given dicalcium phosphate, 1.0 gm., and effervescent sodium phosphate, 4.0 gm., with each meal. By August, 1951, thirty-nine phlebotomies had been performed, with removal of a total of 24 L. of blood. The red blood cell count was 4.1 million, hemoglobin 13.2 gm. per cent, hematocrit forty-four per cent and reticulocytes 4.5 per cent. The liver was palpable 15 cm. below the costal margin; the spleen was not palpable. Liver function tests were normal except for an occasional borderline increase of bromsulphalein retention. The serum iron was 220 μg. per cent.

Between August, 1951, and January, 1952, there was a steady decline in the patient's ability to regenerate blood following phlebotomy and it was necessary to increase the interval between phlebotomies from five days to two to four weeks. The red blood cell count in January, 1952, was 3.0 million, hemoglobin 8.5 gm. per cent and hematocrit 34 per cent. There were no changes in symptoms, physical findings or liver function tests. The serum iron was 40 μg. per cent. Sternal marrow examination was characteristic of iron deficiency anemia. Liver biopsy showed no change in degree of fibrosis but the hemosiderin had disappeared. (Fig. 2.)

Phlebotomies were discontinued in January, 1952. A total of sixty-one had been performed in fourteen months, removing a total of 37 L. of blood (approximately 15 gm. of iron). The administration of phosphates was also stopped at this time. During the next five months the hemogram returned to normal and the serum iron rose to 100 μg. per cent. The glucose tolerance test (intravenous) remained abnormal.

Phosphate administration was resumed in August, 1952, and a single phlebotomy (600 ml.) was performed. This produced a slight anemia (red blood cell count 3.8 million, hemoglobin 13.5 gm. per cent, hematocrit 40 per cent) which slowly disappeared during the next five weeks. By December, 1952, it was necessary to perform four more phlebotomies to maintain the anemia.

CASE II. In 1948 this thirty year old white

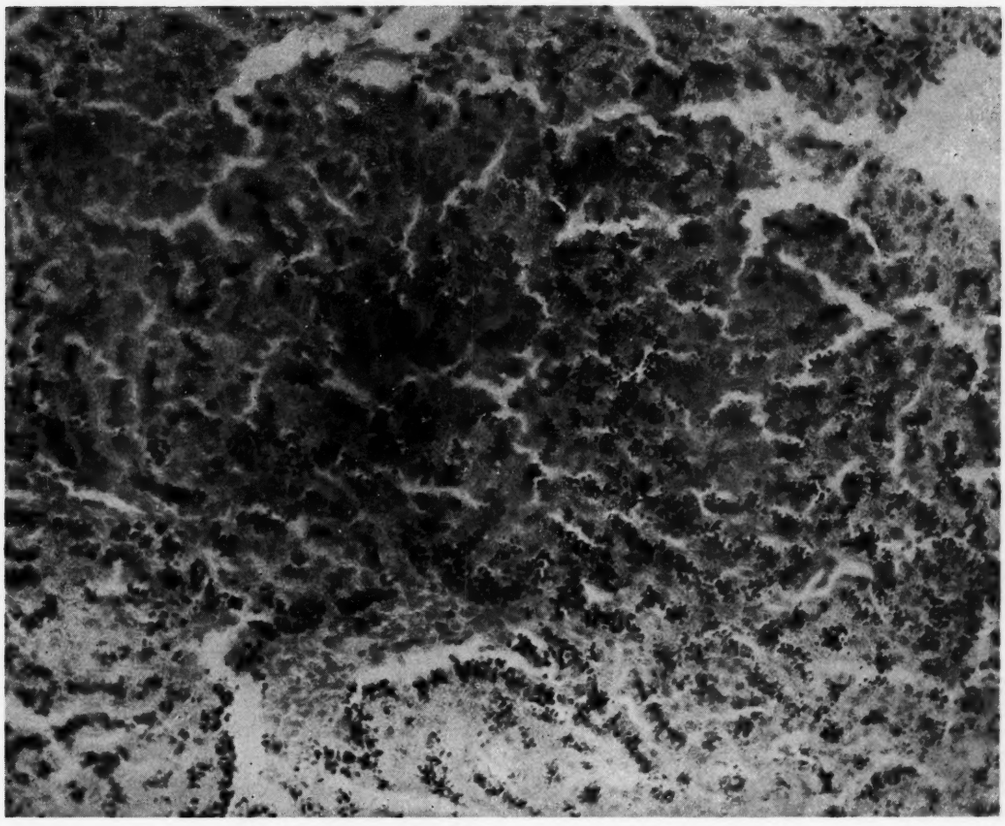


FIG. 3. Case II. Liver biopsy section stained for iron.

man developed jaundice, anorexia and pain in the right upper quadrant of the abdomen. The symptoms and jaundice subsided within a month but episodes of anorexia and epigastric pain continued to appear at irregular intervals. While the patient was in Korea in February, 1951, jaundice and upper abdominal pain recurred. The patient was hospitalized for two months and treated with bed rest and a high protein, high caloric diet. In June, 1951, the patient sustained a penetrating soft tissue wound of the thigh. Débridement of the wound was performed four days after injury. Immediately following surgery the patient experienced anorexia, vomiting and pain in the right upper quadrant of the abdomen. The liver was palpated 2 cm. below the costal margin. These symptoms persisted for approximately six months but liver function tests during this period were normal.

The patient was transferred to Walter Reed Army Hospital in December, 1951, because of continued episodes of fatigue, nausea, vomiting and pain in the right upper quadrant of the abdomen. Alcohol intake had been minimal and the diet had always been adequate. No blood transfusions had been received. The liver was palpated 3 cm. below the costal margin and was tender to percussion. Serum bilirubin, bromsulphalein retention, flocculation tests, serum proteins and alkaline phosphatase were normal. The hemogram was normal; the serum iron was 290 μg. per cent. Needle biopsy of the liver showed a moderate degree of portal fibrosis with no pseudolobulation. There was marked siderosis of the parenchymal cells. (Fig. 3.) Biopsies of skin, gastric mucosa and sternal marrow showed no iron deposits. Hemosiderin granules were found in the urine. The glucose tolerance test was normal.

Controls. The five normal subjects were healthy males twenty to forty years of age. The serum iron levels of this group ranged from 125 to 175 μg. per cent and none of the subjects had anemia.

RESULTS

The amount of iron absorbed by the normal subjects (calculated from the amount not recovered in the feces) was practically identical

with the amount found in the red blood cells. (Table I.) Except for the subject (No. 5) receiving ascorbic acid, the amount of iron absorbed was very small. Serum levels of radioactive iron were undetectable in quantities used

TABLE I
THE FATE OF PHYSIOLOGIC AMOUNTS OF ORALLY ADMINISTERED FERRIC^{59} IRON

Subjects	Gastro-intestinal Absorption (%)	RBC Uptake at 15 Days (%)	Amount in Serum at 2 Hours (%)
Normal			
1 (Feb. 4th)	3.0	1.6	*
(May 28th)	....	1.0	*
2 (Jan. 24th)	2.5	1.6	*
(May 12th)	2.0	1.0	*
3	4.4	4.0	*
4	1.5	3.3	*
5†	6.5	8.0	1.4
Hemochromatosis			
Case I (Mar. 6th)	21.2	21.0	3.0
(June 24th)	20.0	16.6	3.1
Case II	44.7	16.5	5.0

* No radioactivity detectable in quantity used.
† Received 100 mg. ascorbic acid.

in the normal subjects not receiving ascorbic acid.

Case I was first studied three weeks after cessation of phlebotomies. At this time (March of 1952) the serum iron was depressed, the hemogram showed hypochromic anemia and the liver biopsy contained no hemosiderin. (Fig. 2.) The amount of radioactive iron absorbed and the amount present in the red blood cells were identical. These amounts were much greater than normal. Increased absorption was also indicated by the high serum level at two hours. The second study of Case I was made after correction of the anemia (June, 1952). The results parallel the initial study except that some of the radioactive iron absorbed could not be accounted for in the red blood cells at two weeks.

In Case II the amount of iron absorbed was nearly three times as great as the amount found in the red blood cells at two weeks. The very high rate of absorption was again demonstrated by a high radioactive iron level in the serum at two hours.

COMMENTS

Hemochromatosis is classically characterized by extensive deposition of iron throughout the body (particularly the liver, pancreas and skin) and by the clinical triad of cirrhosis of the liver, diabetes mellitus and skin pigmentation. The more common use of needle biopsy of the liver in clinical practice makes it possible to diagnose this disease before the cirrhosis, diabetes or pigmentation occur. This has also been observed in the hemochromatosis of the malnourished South Africans.[18] Thus, although neither of these cases presents the complete clinical triad, it is believed that they both represent early stages of this disease.

Ferrous salts, or ferric salts with added ascorbic acid, have been employed in most studies of iron absorption because they are absorbed more readily than ferric salts alone.[6,7,9,10] Even in iron deficiency states absorption of ferric salts is poor: Moore[9] found less than 6 per cent absorption of ferric ammonium citrate by patients with hypochromic anemia and less than 4 per cent absorption by normals. When ferrous salts were given, the normals still absorbed less than 11 per cent of the iron. Growing children and patients in the last trimester of pregnancy apparently absorb more (10 to 25 per cent) of orally administered ferrous salts.[11,13] In the present study a ferric salt was used so that iron absorption would be small. Also, since dietary iron probably exists in the ferric form, it was thought that the results of this study would be more comparable to those in which natural foods were tagged with radioiron.[19] The iron was given to fasting subjects so that absorption would not be influenced by varying factors in the diet which make iron unavailable for absorption.

In the two recent papers reporting studies of iron absorption in hemochromatosis Fe^{59} was used in the ferrous form.[7,8] In both, the uptake of the radioactive iron in the red blood cells and the amount recovered from the feces were determined. These investigators found increased absorption as indicated by the amount recovered from the feces, but a normal or decreased absorption as measured by the amount utilized for hemoglobin production. These results are in agreement with those of the present study. Another study[6] has been reported in which a patient with hemochromatosis was given ferric^{59} ammonium citrate on two separate occasions. At neither time was an increased absorption

noted; the percentage of iron absorbed, however, was determined only by the red blood cell uptake at one week.

The present study and those previously mentioned[6–8] indicate that the uptake of radioactive iron in red blood cells cannot be used as an index of iron absorption in patients with increased iron stores, and that the only reliable method for measuring iron absorption is by balance technic. This may also hold for other diseases associated with increased iron stores and for conditions manifesting decreased red blood cell production. This observation is probably explained by the fact that absorbed iron goes directly to the liver for storage; none probably moves by way of the intestinal lymph.[20] Thus, when the liver already contains an excessive amount of iron, only a fraction of that recently absorbed will be used immediately for red blood cell production. This is confirmed in part by the studies of Finch et al.[21] who found less than 20 per cent of intravenously injected radioactive iron in the erythrocytes of patients with hemochromatosis, while 70 to 90 per cent was recovered in normals.

The criticism might be made that the patient in Case I no longer had hemochromatosis at the time he was studied. It seems reasonable, however, that although this patient's iron stores had been depleted by numerous phlebotomies the underlying disorder had not been corrected. Some portion of the iron absorbed during the first study might be explained on the basis of hypochromic anemia and decreased iron stores. The absorption of ferric salts, however, by patients with hypochromic anemia due to iron deficiency, even though greater than normal, is small.[9] At the time of the second study, when this patient's anemia had been corrected, the amount of iron absorbed also was increased. Although it may be reasoned that at the time of the second study this patient did not have adequate iron stores, it is thought that this factor should not affect the results. Fontès and Thivolle,[22] using experimental animals, and Finch and his co-workers,[23,24] using humans, have presented data suggesting that after correction of hypochromic anemia replenishment of iron stores normally proceeds slowly.

The fact that one of these patients (Case II) showed an increased absorption of ferric iron in the presence of greatly increased iron stores would seem to indicate that the body need for iron may not necessarily be the controlling factor in the amount of iron absorbed.

The data presented in this and other papers are consistent with recently accepted theories regarding iron metabolism.[25] The following conclusions pertaining to the treatment of hemochromatosis are suggested: (1) The absorption of iron is not necessarily related to body needs. (2) The defect in hemochromatosis is increased absorption of iron. (3) There is no mechanism to provide for the excretion of significant amounts of iron.[26–29] (4) Iron stores may be reduced by multiple phlebotomies.[30] (5) Since treatment by multiple phlebotomies will not prevent continued absorption and deposition of excess quantities of iron, compounds that form unabsorbable iron complexes, such as phosphate salts,[25,31,32] should be administered with meals. Case I demonstrates that phosphate administration alone may not completely prevent the absorption of iron. An iron-free diet is not practical. It is suggested, therefore, that patients with hemochromatosis whose iron stores have been depleted by phlebotomy be maintained by continued phlebotomy and phosphate administration in a state of slight hypochromic anemia.

SUMMARY

1. Tracer quantities of ferric^{59} iron were given orally to two patients with siderosis of the liver. The iron was followed by balance technic, serum levels and red blood cell uptake. Increased amounts (20 to 45 per cent) of the administered iron were absorbed. Four normal subjects similarly studied absorbed 1 to 4 per cent of the iron.

2. In the presence of large amounts of stored iron, the amount of iron absorbed is greater than the amount which appears in the red blood cells. The use of red blood cell uptake of iron as the sole index of absorption is, therefore, not reliable in studies of such patients.

3. Successful removal of stored iron by phlebotomy has been demonstrated in one patient with hemochromatosis. Further studies on this patient indicate that the administration of phosphate salts will not completely inhibit the absorption of excessive amounts of iron.

4. It is suggested that, following removal of stored iron, patients with hemochromatosis be maintained by continued phlebotomy and phosphate administration in a state of slight hypochromic anemia.

REFERENCES

1. McCance, R. A. and Widdowson, E. M. Absorption and excretion of iron. *Lancet*, 2: 680–684, 1937.
2. McClure, C. W. Iron metabolism in a case of hemochromatosis. *Arch. Int. Med.*, 22: 610–616, 1918.
3. Dry, T. J. Hemochromatosis; its relation to the metabolism of iron. *Proc. Staff Meet., Mayo Clin.*, 8: 56–59, 1933.
4. Widdowson, E. M. and McCance, R. A. Absorption and excretion of iron before, during, and after period of very high intake. *Biochem. J.*, 31: 2029–2032, 1937.
5. Gram, M. R. and Leventon, R. M. Iron absorption by women: comparison of three ferrous salts. *J. Lab. & Clin. Med.*, 39: 871–873, 1952.
6. Balfour, W. M., Hahn, P. F., Bale, W. F., Pommerenke, W. T. and Whipple, G. H. Radioactive iron absorption in clinical conditions: normal, pregnancy, anemia, and hemochromatosis. *J. Exper. Med.*, 76: 15–31, 1942.
7. Dubach, R., Callander, S. T. and Moore, C. V. Studies in iron transportation and metabolism. VI. Absorption of radioactive iron in patients with fever and with anemias of varied etiology. *Blood*, 3: 526–540, 1948.
8. Alper, T., Savage, D. V. and Bothwell, T. H. Radioiron studies in a case of hemochromatosis. *J. Lab. & Clin. Med.*, 37: 665–675, 1951.
9. Moore, C. V., Dubagh, R., Minnich, V. and Roberts, H. K. Absorption of ferrous and ferric radioactive iron by human subjects and by dogs. *J. Clin. Investigation*, 23: 755–767, 1944.
10. Hahn, P. F., Jones, E., Lowe, R. C., Meneely, G. R. and Peacock, W. The relative absorption and utilization of ferrous and ferric iron in anemia as determined with the radioactive isotope. *Am. J. Physiol.*, 143: 191–197, 1945.
11. Darby, W. J., Hahn, P. F., Koster, M. M., Steinkamp, R. C., Densen, P. M. and Cook, M. B. The absorption of radioactive iron by children 7 to 10 years of age. *J. Nutrition*, 33: 107–119, 1947.
12. Sharpe, L. M., Peacock, W. C., Cooke, R. and Harris, R. S. The effect of phytate and other food factors on iron absorption. *J. Nutrition*, 41: 433–466, 1950.
13. Hahn, P. F., Carothers, E. L., Darby, W. J., Martin, M., Sheppard, C. W., Cannon, R. O., Beam, A. S., Densen, P. M., Peterson, J. C. and McClellan, G. S. Iron metabolism in human pregnancy as studied with the radioactive isotope Fe^{59}. *Am. J. Obst. & Gynec.*, 61: 477–486, 1951.
14. Peterson, R. E. Separation of radioactive iron from biological materials. *Anal. Chem.*, 24: 1850–1851, 1952.
15. Peterson, R. E. An improved spectrophotometric procedure for the determination of serum iron, using 4, 7-diphenyl-1, 10-phenanthroline. (To be published.)
16. Rath, C. E. and Finch, C. A. Chemical, clinical and immunological studies on the products of human plasma fractionation. XXXVIII. Serum iron transport measurement of iron-binding capacity of serum in man. *J. Clin. Investigation*, 28: 79–85, 1949.
17. Rath, C. E. and Finch, C. A. Sternal marrow hemosiderin. *J. Lab. & Clin. Med.*, 31: 81–86, 1948.
18. Gillman, J., Mandelstam, J. and Gillman, T. Comparison of chemical and histological estimations of iron and copper content of the livers of Africans in relation to the pathogenesis of cytosiderosis and cirrhosis (Hemochromatosis). *South African J. M. Sc.*, 10: 109–136, 1945.
19. Moore, C. V. and Dubach, R. Observations on the absorption of iron from foods tagged with radioiron. *Tr. A. Am. Physicians*, 64: 245–256, 1951.
20. Peterson, R. E. and Mann, J. D. Transport of radioactive iron in the intestinal lymph. *Am. J. Physiol.*, 169: 763–766, 1952.
21. Finch, C. A., Gibson, J. G., Peacock, W. C. and Fluharty, R. G. Iron metabolism. Utilization of intravenous radioactive iron. *Blood*, 4: 905–927, 1949.
22. Fontès, G. and Thivolle, L. Réchèrches expérimentales sur la thérapeutique de l'anémie grave par carence martiale et notamment par hémorragie; la reconstitution des réserves martiales. *Sang*, 10: 144–147, 1936.
23. Finch, S., Haskins, D. and Finch, C. A. Iron metabolism. Hematopoiesis following phlebotomy. Iron as a limiting factor. *J. Clin. Investigation*, 29: 1078–1082, 1950.
24. Haskins, D., Stevens, A. R., Finch, S. and Finch, C. A. Iron metabolism. Iron stores in man as measured by phlebotomy. *J. Clin. Investigation*, 31: 543–547, 1952.
25. Granick, S. Iron metabolism and hemochromatosis. *Bull. New York Acad. Med.*, 25: 403–428, 1949.
26. Peterson, R. E. Radioiron excretion in humans. (Unpublished observations.)
27. Hahn, P. F., Bale, W. F., Hetting, R. A., Kamen, M. D. and Whipple, G. H. Radioactive iron and its excretion in urine, bile and feces. *J. Exper. Med.*, 70: 443–451, 1939.
28. Greenberg, D. M., Copp, D. H. and Cuthbertson, E. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. VII. The distribution and excretion particularly by way of the bile of Fe, Co, Mn. *J. Biol. Chem.*, 147: 749–756, 1943.
29. Copp, D. H. and Greenberg, D. M. A tracer study of iron metabolism with radioactive iron. *J. Biol. Chem.*, 164: 377–387, 1946.
30. Davis, W. D. and Arrowsmith, W. R. The effect of repeated phlebotomies in hemochromatosis. *J. Lab. & Clin. Med.*, 39: 526–532, 1952.
31. Moore, C. V., Arrowsmith, W. R., Welch, J. and Minnich, V. Studies in iron transportation and metabolism. IV. Observations on the absorption of iron from the gastro-intestinal tract. *J. Clin. Investigation*, 18: 553–580, 1939.
32. Hegsted, D. M., Finch, C. A. and Kinny, T. D. The influence of diet on iron absorption. II. The interrelation of iron and phosphorus. *J. Exper. Med.*, 90: 147–156, 1949.

Metabolic Studies in Gout with Emphasis on the Role of Electrolytes in Acute Gouty Arthritis*

MELVIN H. LEVIN, M.D., J. BERNARD RIVO, M.D. *and* SAMUEL H. BASSETT, M.D.
Los Angeles, California

THE relationship of gouty arthritis to adrenal cortical function has been the subject of intensive investigation and speculation in recent years.[1–5] Our views on this subject have been discussed in a previous communication[6] reporting the results of a number of adrenal cortical tests on gouty subjects under various conditions. The data derived from this study failed to support the thesis that temporary hypofunctioning of the "pituitary-adrenal system" is causally related to the onset of acute gouty arthritis.

Because most previous studies measured so-called "glucocorticoid" function, additional data on the "mineralocorticoid" activity of the adrenal cortex in gout seemed needed, particularly since the prodromal diuresis of sodium, chloride and water in gout originally described by Talbott et al.[7] has been recently interpreted to be a strong argument linking acute gout to decreased adrenal activity.[3,4] In an effort to clarify the relation between gouty arthritis and electrolyte metabolism, three patients, two with pretophaceous gouty arthritis and one normal control,† were studied.

Metabolic balances for nitrogen, sodium, potassium and chloride, plus occasional determinations of urinary reducing corticoids, were performed in one gouty patient (A. McG.) for ninety days, including observations during interval gout, acute spontaneous gouty arthritis, ACTH and testosterone administration, steroid-induced gout and colchicine therapy. The second patient (L. H.) and the normal control subject (A. N.) were studied for 161 and 59 days, respectively, while on a chloride balance regimen, with additional observations on serum and urinary uric acid and circulating eosinophils. Basal observations plus the effects of mercurial diuretics and colchicine were made in the control subject, while the effects of mercurial diuretics, colchicine, ACTH and pitressin were studied in the gouty patient.

† The normal control subject (A. N.) and the second gouty patient (L. H.) were mild diabetics well controlled by diet alone.

METHODS

Eosinophil counts were performed by the method of Dunger[8] with modifications as suggested by Thorn et al.[9] Uric acid was estimated by a modification of the Kalckar method.[10] Reducing corticoids were determined by the method of Heard, Sobel and Venning.[11] Aliquots of diet, feces, urine and emesis were ashed in a muffle furnace at a temperature not exceeding 450°C. Sodium and potassium determinations were performed directly on diluted specimens of serum and urine, using the Beckman flame photometer. Nitrogen was determined by the Hiller, Plazin and Van Slyke modification of the Kjeldahl procedure;[12] and chlorides by a modification of the Volhard silver nitrate-ammonium thiocyanate titration.[13–15]

RESULTS

CASE 1. A. McG. The data for this patient with gouty arthritis are depicted in Figures 1 to 3. During the ninety-day study seven attacks of acute gout were observed. The third and fourth gouty episodes were considered ACTH-induced because of their temporal relation to ACTH withdrawal. The seventh attack was considered related to testosterone withdrawal. The remainder of the attacks have been classified as spontaneous.

* From the Veterans Administration Center, Los Angeles, Calif., and the Department of Medicine, School of Medicine, University of California Medical Center, Los Angeles, Calif.

Spontaneous gout: As noted in Figure 1, sodium and chloride diuresis, possibly representing hypocorticalism, never preceded the spontaneous episodes. The slight negative sodium and chloride balance that was observed with the first, second and sixth attacks invariably occurred temporally associated with the expected brisk diuresis of sodium and chloride. This diuresis, suggestive of temporary hypocorticalism, was never duplicated during spontaneous gouty episodes.

Transient periodic shifts to slightly negative

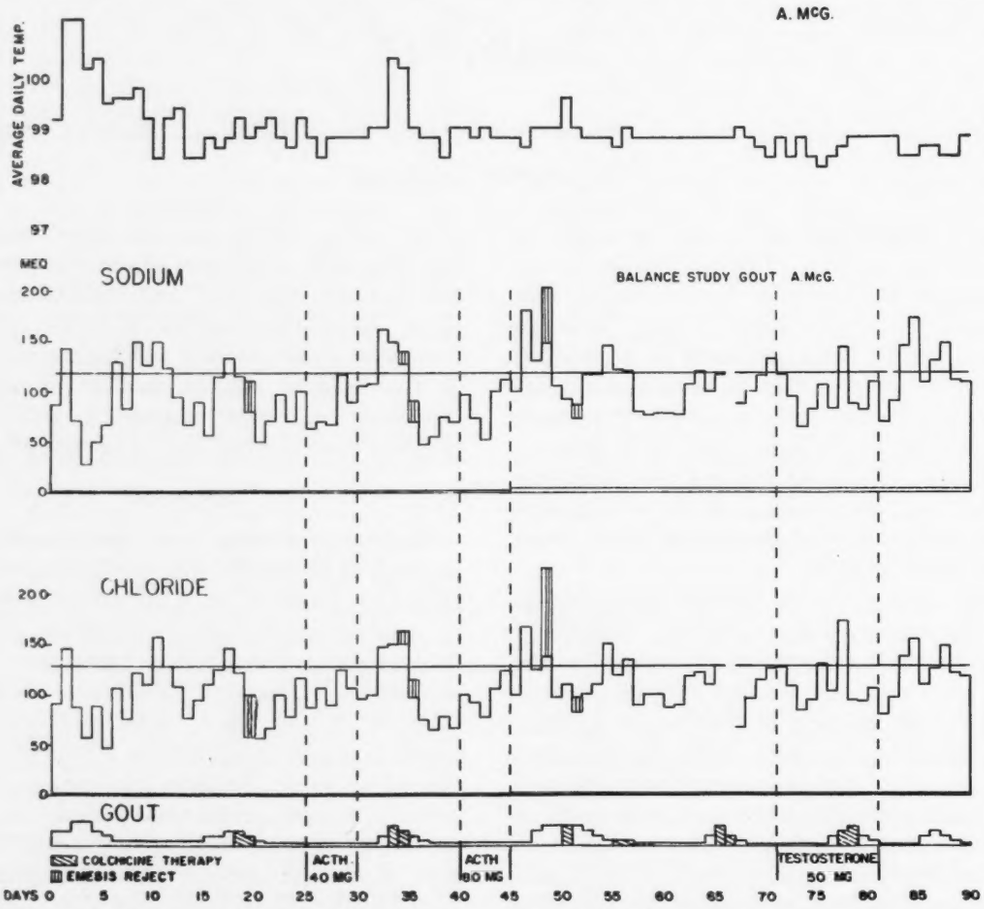


FIG. 1. (A. McG., gouty subject.) Daily sodium and chloride balances, with temperature curve and gout attack indicated. The level of sodium and chloride intake is indicated by the straight line at 137 and 130 mEq., respectively. Fecal loss is indicated by the line just above the baseline; urinary output by the irregular line, and rejections or emesis by the striped area above the urinary line. The daily output is plotted so that there is a summation of urinary, fecal and emesis-rejection output. Extension of this above the intake indicates negative balance; where it falls below intake the balance is positive. Gouty attacks are indicated below the chloride balance. The height of the block indicates the severity of the attack. Colchicine administration is indicated by the lined blocks depicting the gouty episodes. *Note:* (1) lack of sodium and chloride diuresis preceding spontaneous attacks and the definite diuresis with post-ACTH attacks; (2) rapid return to positive balance within one to three days after onset of post-ACTH diuresis; (3) steady positive balance from days 57 to 77 while two gouty attacks occurred; (4) sodium and chloride retention following colchicine therapy.

after the gouty attacks were well established. The fifth and sixth attacks developed after periods of seven and nine days, respectively, of steady positive electrolyte balance. In sharp contrast are the findings during the two post-ACTH attacks. These occurred on the third day following interruption of ACTH and were sodium and chloride balance were noted only during the early portion of this study (days 1–19). Later (days 57–75) relatively long periods of steady sodium and chloride balance were observed. As depicted in Figure 2, moderate temperature elevation and marked weight reduction were observed during the early por-

tion of the study. The later period of stable electrolyte balance was associated with normal temperature and a relatively constant weight curve. In spite of steady electrolyte balance, gouty arthritis continued to develop (fifth and sixth attack, Fig. 1).

ACTH effects: The marked electrolyte retention during ACTH therapy and the subsequent rapid return toward balance within one to three days after the onset of the post-ACTH diuresis points to relatively normal ACTH response.

Nitrogen and potassium balances are illus-

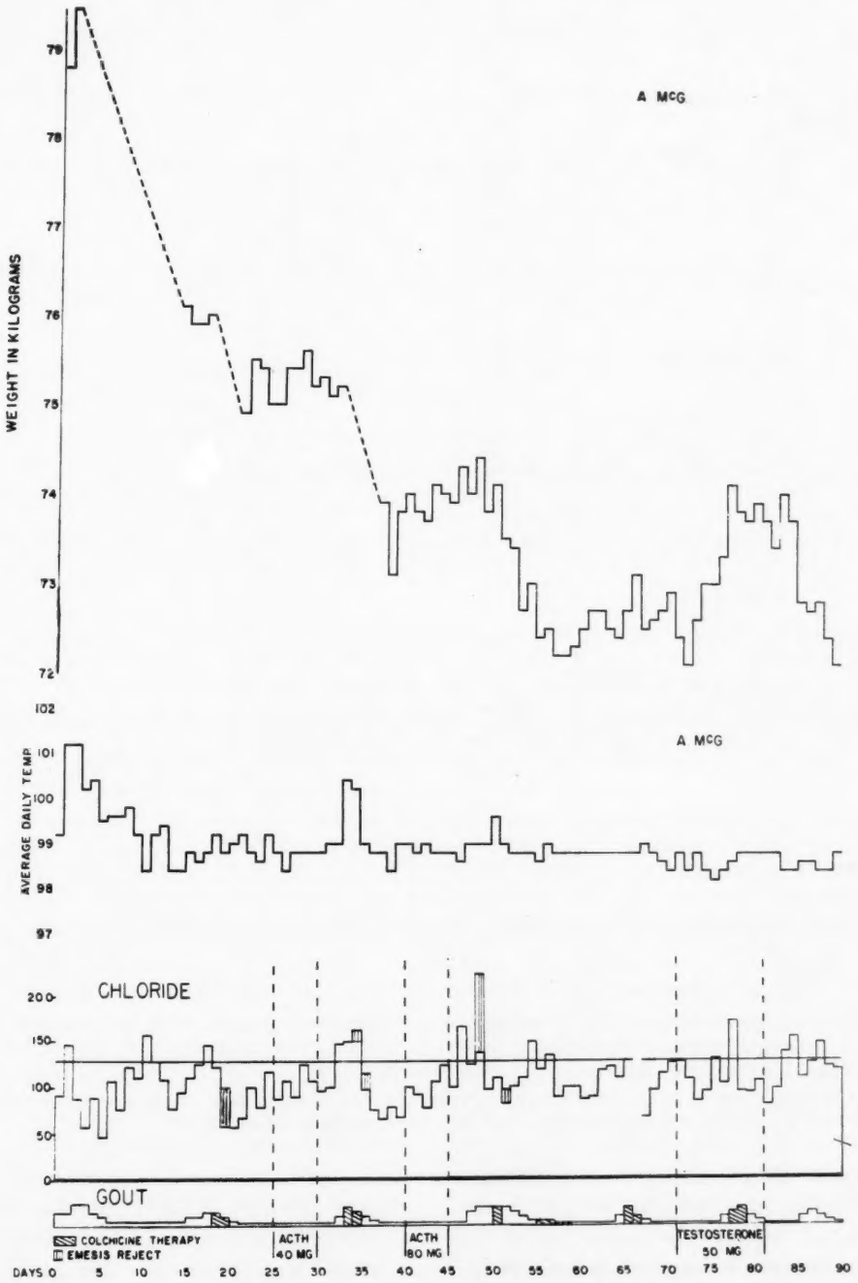


FIG. 2. (A. McG., gouty subject.) Daily chloride balance, with weight and temperature curves. *Note:* (1) minor oscillations in chloride balance during early portion of the study associated with temperature elevation and rapid weight loss; (2) relatively stable temperature and weight curves during days 55 to 70 associated with persistently positive chloride balance. During this period a spontaneous attack of acute articular gout developed (days 64 to 67).

trated in Figure 3. In general, nitrogen and potassium balances tended to parallel one another; the over-all trend was one of definite negative balance for the early period of study, essential equilibrium for the mid-portion and positive balance for the latter period. No consistent changes in either nitrogen or potassium were noted during the attacks or upon the administration of colchicine. The effect of ACTH upon nitrogen balance was one of insignificant change for the five days during which 40 mg. per day were given. The total nitrogen balance for five days preceding ACTH was −1.97 gm. as contrasted to +1.89 gm. during this therapy. With the dose of 80 mg. per day the values for total nitrogen balance for five days of control and treatment were +4.17 and −4.21 gm., respectively. The total potassium balance for the 40 and 80 mg. per day of ACTH therapy was 0 and +13 mEq., respectively. However, the definite retention of +79 and +92 mEq. of potassium, respectively, during the post-ACTH five-day period is good evidence of a strong ACTH effect.

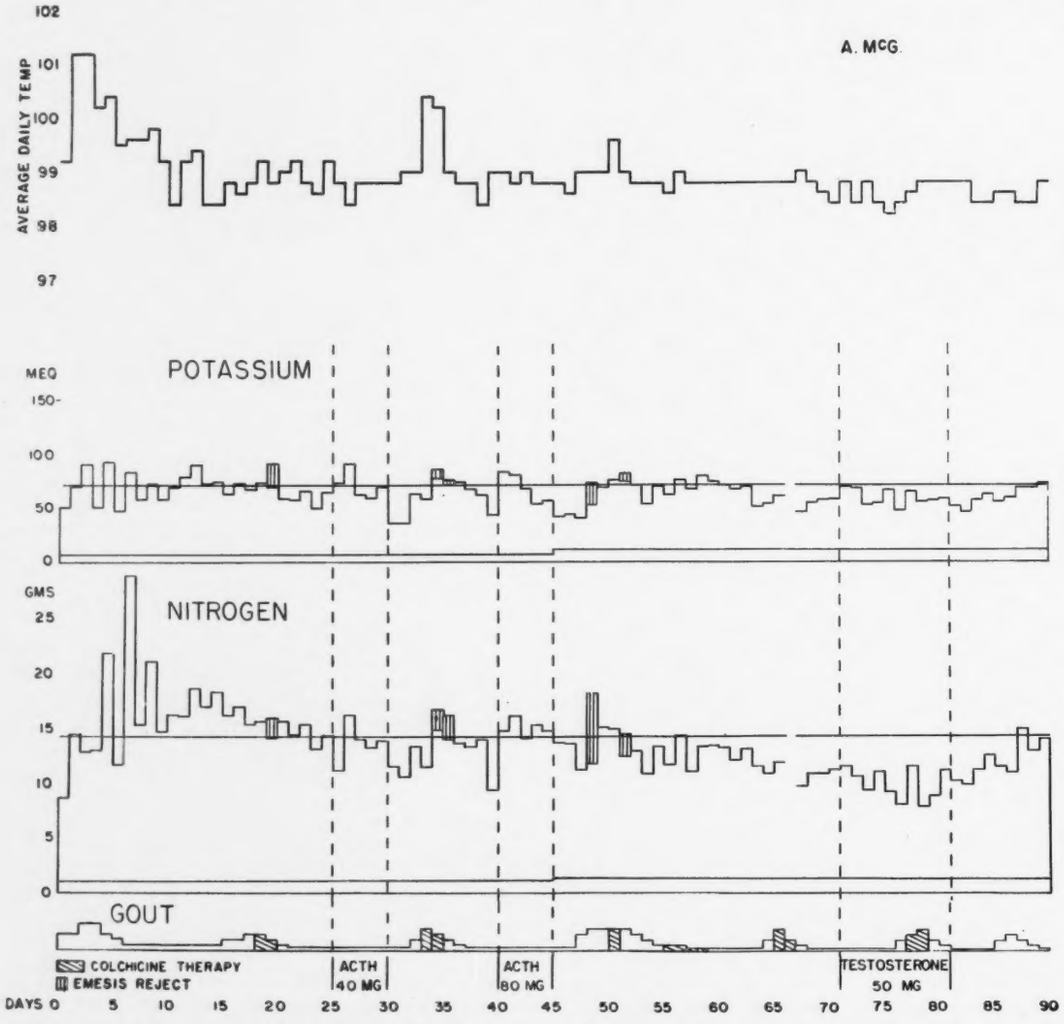


FIG. 3. (A. McG., gouty subject.) Daily potassium and nitrogen balances, with temperature curve and gout attacks indicated. Method of plotting as in Figure 1. *Note:* (1) retention of potassium each time after ACTH is withdrawn and the absence of this finding with spontaneous gouty attacks; (2) lack of definite change in nitrogen balance with acute gouty arthritis; (3) lack of significant change in potassium or nitrogen balance with colchicine administration. See text for remainder of discussion.

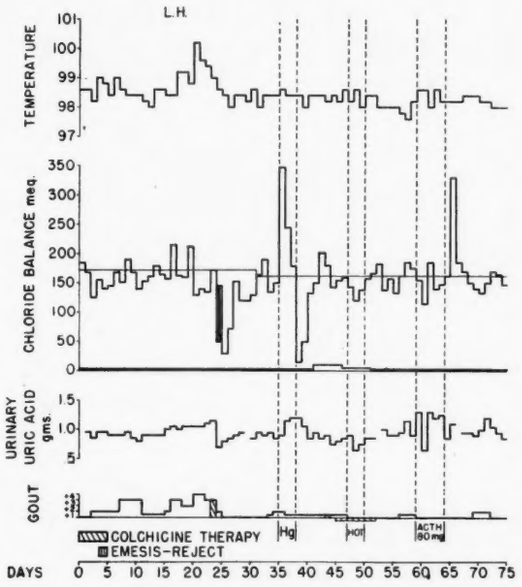
Response to testosterone and colchicine: A daily dose of 50 mg. of testosterone propionate moderately exaggerated the already positive balance of potassium and nitrogen. A moderate diuresis followed its withdrawal and heralded the onset of the seventh attack of gout, although

no definite sodium and chloride effects were observed during testosterone treatment.

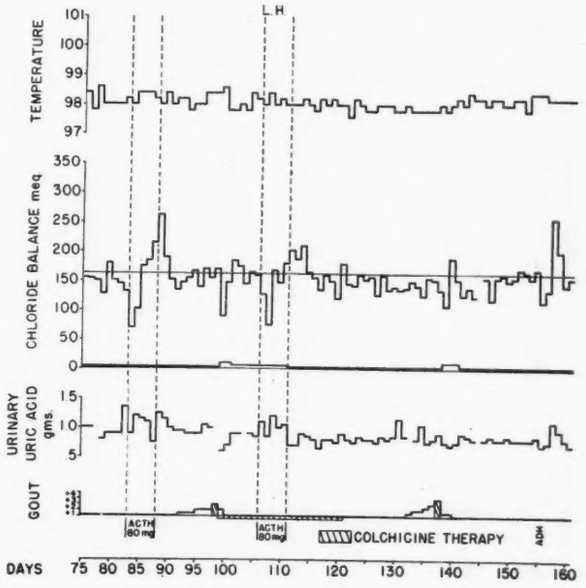
The effect of colchicine, given hourly for acute gouty arthritis in total daily oral doses of 4.5 to 8 mg., is illustrated in Figure 1. Definite although transient sodium and chloride retention occurred within forty-eight hours of the initial administration of this drug. This was due to decreased urinary sodium and chloride concentration without significant change in urinary volume. Prompt relief from the articular manifestations of the disease followed colchicine therapy.

Serum sodium, chloride and potassium studies performed every five days revealed no significant changes. The excretion of urinary reducing corticoids was at essentially normal baseline values which approximately doubled with both courses of ACTH. Random determinations about once every five days revealed no essential difference between the basal state and acute attacks. Colchicine did not appear to alter this finding.

Case II. L. H. The data for the second subject with gouty arthritis are presented in Figures 4A, 4B and 5. During the 161 days of observation seven attacks of acute gouty arthritis occurred; two attacks, the fifth and sixth, followed ACTH withdrawal while the remaining five episodes were spontaneous.



4A



4B

Fig. 4A. (L. H., gouty subject.) Chloride balance, temperature curve and uric acid excretion for the first seventy-five days. The balance data are plotted in the same manner as in Figure 1. *Note:* (1) massive diuresis produced by mercuhydrin, 2 cc. intramuscularly for three days (Hg), without exacerbation of the mild gout attack that developed two days before injection; (2) chloride retention associated with warm weather (HOT); this probably represents excessive skin loss of chloride; (3) normal ACTH response and rapid rebound adjustment after ACTH withdrawal; an acute gouty episode developed five days after ACTH interruption; (4) chloride retention after colchicine on twenty-fourth and forty-third day.

Fig. 4B. (L. H., gouty subject.) Continuation of study depicted in Figure 4A. *Note:* (1) rapid return to approximate chloride balance within three days after ACTH withdrawal, followed by acute gouty attack; (2) prolongation of post-ACTH diuresis of chloride while on maintenance colchicine (days 111–114) with no gouty attack following; (3) chloride retention after colchicine administration; (4) moderate chloride retention after pitressin (ADH) followed by compensatory diuresis; (5) lack of spontaneous chloride diuresis with acute spontaneous gouty episodes.

Spontaneous gout: Chloride diuresis of significant magnitude did not precede any spontaneous gouty attack but substantial negative chloride balance occurred several times following drug administration (ACTH, pitressin, mercurials). Minor negative chloride balance preceded the first three spontaneous attacks. Quantitatively, however, these changes were of small magnitude and occurred during a period of brisk weight loss and moderate fever. (Fig. 4A.) Later, (days 120–139, Fig. 4B) long periods of essential chloride equilibrium were observed,

accompanied by normal temperature and relatively steady weight. During this period acute gouty attacks continued. The fourth and seventh gouty episodes developed after three and eleven days, respectively, of positive chloride balance.

depicted in Figures 4A and B. This was occasionally associated with a reduction in urinary volume. Urinary chloride concentration regularly fell after colchicine therapy. Daily fecal loss of chloride increased only by 7 to 9 mEq. during colchicine-induced diarrhea so

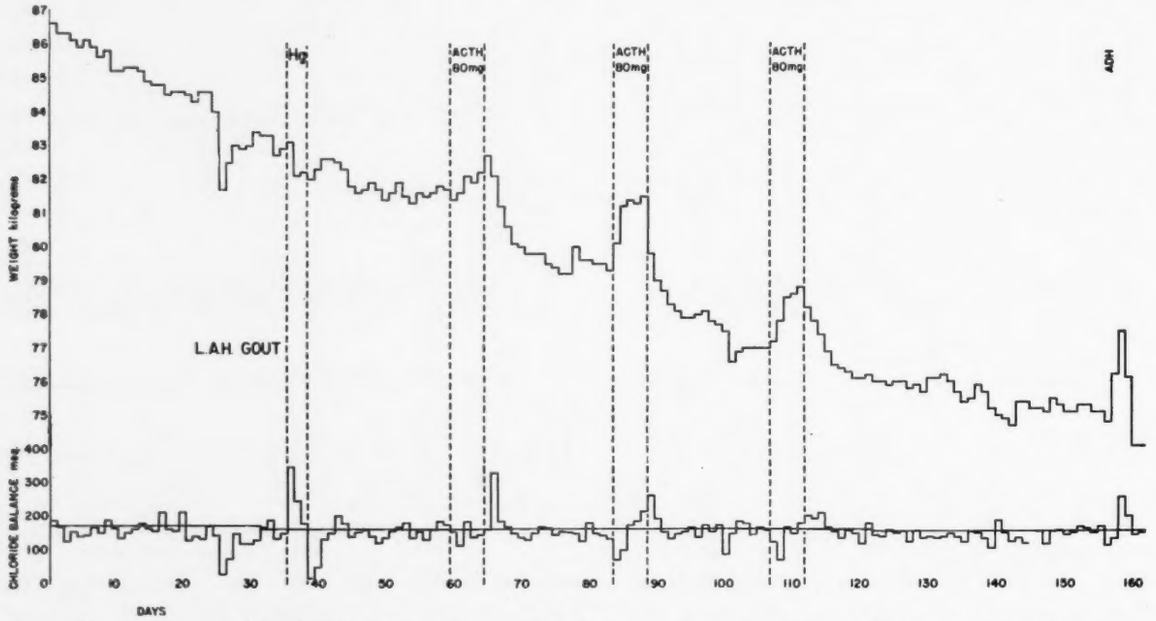


FIG. 5. (L. H., gouty subject.) Chloride balance and weight curve. *Note:* (1) minor variations in chloride balance during early period associated with weight loss; (2) relatively stable chloride balance and weight curve during days 115–140. As noted in Figure 4B, a gout attack developed on the 132nd day.

ACTH effects: ACTH was administered intramuscularly on three occasions in divided doses of 80 mg. per day for five days. (Figs. 4A and B.) The last course of ACTH was preceded, accompanied and followed by "prophylactic" colchicine (0.5 mg. three times per day).

With each administration of ACTH sharp chloride retention occurred, followed by the usual diuresis. Counter-regulatory phenomena were suggested by the rapid post-ACTH return toward approximate chloride balance. This was less evident after the last course of ACTH while the patient was receiving "prophylactic" colchicine. On this occasion the post-ACTH diuresis was more prolonged than usual, possibly indicating more marked pituitary suppression, yet gouty arthritis failed to appear. Articular gout did ensue following the first and second ACTH withdrawals in spite of evidence of rather prompt recovery of adrenal function.

Response to colchicine, pitressin and mercuhydrin: Colchicine was administered orally on four occasions in total doses of 5 to 8 mg. Moderate to marked chloride retention followed, as that the reduction in urinary chloride was not due to fecal excretion.

Pitressin tannate in oil, 0.5 cc., was injected intramuscularly on the 155th day. This was followed by a marked retention of water and a moderate retention of chloride. The effect lasted two days followed by compensatory diuresis of water and chloride.

Mercuhydrin, 2 cc., was administered intramuscularly daily from the thirty-fifth through the thirty-seventh day. In spite of the marked diuresis of chloride that ensued acute gouty arthritis did not follow.

Data obtained throughout this study revealed definite uricosuria, concomitant with a decrease in serum uric acid and circulating eosinophils, following ACTH. Strong "rebound" effects were observed in these parameters. No significant alterations were noted during spontaneous gouty attacks. Colchicine produced no consistent ACTH-like effects upon these uric acid or eosinophil levels. Serum chloride determinations remained within the normal range throughout the study.

CASE III. A. N. Figure 6 depicts the results of a forty-nine-day study of the control subject. As in the two gouty patients, that period of observation associated with moderate weight loss was accompanied by frequent minor oscillations of chloride balance. Fever was absent throughout the study.

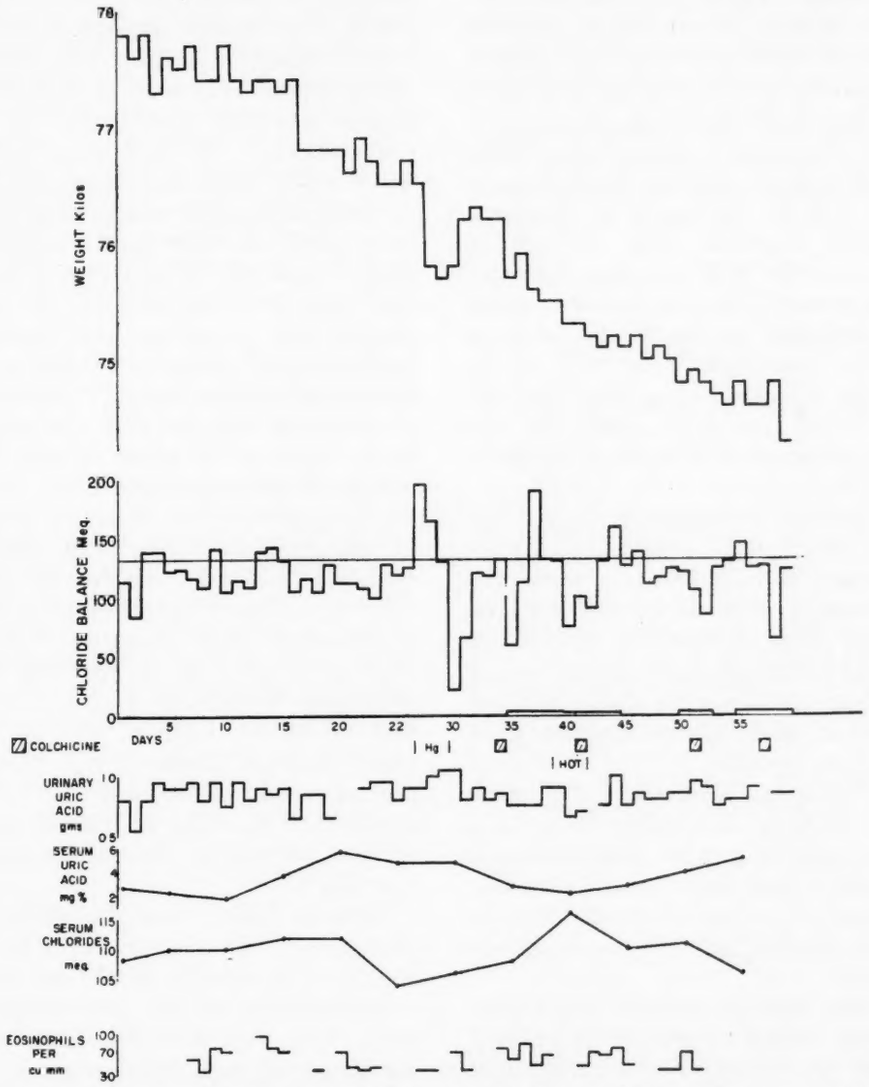


FIG. 6. (A. N., normal control subject.) Chloride balance, weight curve, uric acid and eosinophil data. Data plotted in the same manner as in Figures 1 to 5. *Note:* (1) minor oscillations in chloride balance throughout study, associated with declining weight; (2) colchicine administrations were followed by chloride retention except on the forty-first day when the patient was already conserving urinary chloride, associated with hot weather (HOT).

Colchicine, administered in total oral doses of 5 or 6 mg., produced moderate to striking chloride retention. Urinary volume was relatively stable while urinary chloride concentration was decreased by this drug. Stool loss of chloride increased only from 1.3 mEq. per day during basal conditions to a maximum of 5.4 mEq. during colchicine-induced diarrhea. Therefore the change in urinary chloride was not due to increased fecal loss. Colchicine exerted no effect on the chloride balance when given on the forty-first day. This might be explained by the associated period of hot weather (indicated by HOT, Fig. 6).

No significant changes in circulating eosinophils, blood and urine uric acid and serum chloride were observed, except for an unex-

plained elevated serum chloride (116 mEq. on the fortieth day) which occurred during the spell of hot weather.

COMMENTS

Spontaneous Gout. These data suggest that demonstrable change in the "mineralocorticoid" activity of the pituitary-adrenal system, with particular reference to hypofunction, is not essential in the development of acute gouty arthritis. Of the nine spontaneous gouty attacks studied none was associated with electrolyte or other changes indicative of decreased adrenal cortical function. The findings in spontaneous gout did not resemble those observed in the post-ACTH gouty attacks which admittedly, although probably not due to hypocorticalism, were associated with it. In this respect our data do not support the contention that acute gout is "a deficiency disorder, the immediate cause of which is persistent corticoid lack."[4]

It was not possible to corroborate the concept of a "gouty cycle" with respect to electrolytes.[7,16] Not only did we fail to observe any regularly occurring diuresis of sodium and chloride in gouty patients but the occasionally observed negative balance was transient and of small magnitude. At no time did significant diuresis of sodium and chloride precede acute spontaneous gouty arthritis.

Newburgh[17] has pointed out that obese patients on a reduction diet exhibit irregularly occurring decreases in weight, associated with varying periods of diuresis. It seems likely that the minor electrolyte variations seen in the early portion of these studies were due to the associated weight loss.

Since a similar chloride pattern was evident in the non-gouty control subject during a period of weight loss, the minor chloride alterations observed in the gouty subjects are not particularly impressive.

Response to ACTH and Withdrawal from ACTH. In the doses used ACTH appeared to exert the expected effect upon sodium, chloride and potassium in our subjects. Likewise, the data on eosinophils, uric acid and urinary corticoids followed the now well documented pattern.[5,18,19,20] The only parameter of adrenal function utilized which failed to respond was the nitrogen balance on the 40 mg. per day ACTH schedule. However, even here, with the 80 mg. dose a definite though moderate effect was observed. Apparently, gouty patients are capable of responding in the usual way to ACTH.

The data concerning recovery from ACTH withdrawal is of particular interest since it has been claimed that failure to recover from temporary adrenal lack due to deficient "rebound regulatory" activity is an important event leading to post-ACTH gout.[1,3] In our earlier report on adrenal function in gout it was pointed out that, with respect to "glucocorticoid" activity, the response to ACTH and its withdrawal appeared to be normal; moreover, no significant differences in response to ACTH were noted in those gouty subjects who developed post-ACTH attacks and those who did not.[6] The data derived from the present study support this contention with respect to "mineralocorticoid" function. Utilizing all of the parameters studied, evidence of prompt recovery of adrenocortical function was present in the gouty subjects. In spite of this, post-ACTH attacks developed in four of five instances. The lone exception occurred in patient L. H. while he was given colchicine prophylactically. It is significant that with this dose of colchicine the chloride balance appeared to remain in the hypocortical range (negative balance) longer than previously. Thus the sole example of decreased "rebound" activity was the only time ACTH withdrawal was *not* followed by gouty arthritis. Apparently, other factors at present poorly understood may be of greater significance than the activity of the pituitary-adrenal system in the pathogenesis of acute articular gout.

Colchicine Effect. The mechanism of action of colchicine in acute gouty arthritis remains an enigma. The drug was without significant or constant effect on the tests measured in this study with one exception—the sodium and chloride balance. Colchicine resulted in moderate to marked sodium and chloride retention in both the gouty and the control subjects. This effect was variable but of sufficient regularity and degree to provoke interest although no plausible explanation for it is apparent. The possibility that the electrolyte changes resulted from increased activity of the pituitary-adrenal "system" seems unlikely since the remainder of the metabolic data reflect no evidence of such an effect. This is particularly evident upon comparing the metabolic effects of colchicine and ACTH on the gouty subjects. (Figs. 1, 4A and B.) Previous observations in

this and other laboratories have likewise suggested that the therapeutic effect of colchicine is unrelated to stimulation of endogenous pituitary activity.[3,6]

Although fecal chloride studies seem to rule out stool loss of sodium and chloride as an explanation for the observed colchicine effect, one other possibility exists. The retention of chloride was at times roughly proportional to the decrease in urinary volume. It remains possible that the diarrhea produced by colchicine may have been in part responsible for the decreased urinary volume and associated decrease in sodium and chloride excretion. Extension of these preliminary observations is necessary before more precise interpretation is possible.

Other Drugs. The observation that the marked diuresis of salt and water provoked by mercurial diuretics was not followed by acute gouty arthritis is of course inconclusive. Others have reported that diuretics may provoke acute gout.[2,21]

Pitressin was administered to compare its effect in gout with that of colchicine and ACTH. Although pitressin produced retention of both water and chloride, quantitatively the change in water balance was proportionately greater than that of chloride. This difference suggested that the action of colchicine on electrolytes was probably not mediated through a pitressin-like effect on the renal tubules.

Testosterone propionate appeared to exert little metabolic effect in the one gouty patient who received it. Its withdrawal was followed by moderate sodium and chloride diuresis and an attack of podagra. The induction of post-testosterone gout has been seen by us in five of nine attempts.[6] The mechanisms responsible for this phenomenon are unknown.

SUMMARY AND CONCLUSIONS

1. Data derived from metabolic balance studies and adrenal function tests in two gouty patients and one normal control subject are presented. Special emphasis was placed upon investigation of the "mineralocorticoid" activity of the adrenal cortex in gout.

2. Patients with gout appeared to respond normally to ACTH and its withdrawal in respect to the parameters studied.

3. No evidence was uncovered to support the concept that acute gout is fundamentally related to temporary pituitary-adrenal deficiency.

4. The association of sodium and chloride diuresis with gouty arthritis was inconstant. The body weight curve appears to influence electrolyte exchange. A significant cyclic electrolyte variation in gout was not observed.

5. Therapeutic doses of colchicine are followed by sodium and chloride retention. The mechanisms underlying this effect are unknown but merit further study.

Acknowledgment: We are greatly indebted to Frances Davis, Tomoko Fukui, William McCandless, Pauline E. Schatz and Betty Yost for technical assistance.

REFERENCES

1. Robinson, W. D., Conn, J. W., Block, W. D. and Louis, L. H. Role of the adrenal cortex in urate metabolism and in gout. *J. Lab. & Clin. Med.*, 33: 1473, 1948.
2. Hellman, L. Production of acute gouty arthritis by adrenocorticotrophin. *Science*, 109: 280, 1949.
3. Wolfson, W. Q. and Cohn, C. The role of the pituitary adrenocorticotrophic hormone (ACTH) and of adrenal cortical steroid hormones in the pathological physiology and experimental therapeutics of clinical gout, p. 241. In Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote. Philadelphia, 1950. Blakiston Co.
4. Wolfson, W. Q., Hunt, H. D., Cohn, C., Robinson, W. D. and Duff, I. F. ACTH and colchicine in the clinical treatment of acute gouty arthritis: physiological considerations and review of therapeutic results in 51 attacks, *J. Michigan M. Soc.*, 49: 1058, 1950.
5. Gutman, A. B. and Yü, T. F. Effects of adrenocorticotrophic hormone (ACTH) in gout. *Am. J. Med.*, 9: 24, 1950.
6. Levin, M. H., Fred, L. and Bassett, S. H. Metabolic studies in gout. *J. Clin. Endocrinol.*, 12: 506, 1952.
7. Talbott, J. H., Jacobson, B. M. and Oberg, S. A. The electrolyte balance in acute gout. *J. Clin. Investigation*, 14: 411, 1935.
8. Dunger, R. Eine einfache Methode der Zahlung der eosinophilen Leukozyten und der praktische Wert dieser Untersuchung. *München. med. Wchnschr.*, 57: 1942, 1910.
9. Thorn, G. W., Forsham, P. H., Prunty, F. T. G. and Hills, A. G. A test for adrenal cortical insufficiency: response to pituitary adrenocorticotrophic hormone. *J. A. M. A.*, 137: 1005, 1948.
10. Kalckar, H. M. Differential spectrophotometry of purine compounds by means of specific enzymes. *J. Biol. Chem.*, 167: 429, 1947.
11. Heard, R. D. H., Sobel, H. and Venning, E. H. The neutral lipide-soluble reducing substances of urine as an index of adrenal cortical function. *J. Biol. Chem.*, 165: 699, 1946.
12. Hiller, A., Plazin, J. and Van Slyke, D. D. A study of conditions of Kjeldahl determination of nitrogen in proteins. *J. Biol. Chem.*, 176: 1401, 1948.

13. Eisenman, A. J. A note on the Van Slyke method for the determination of chlorides in blood and tissue. *J. Biol. Chem.*, 82: 411, 1929.
14. Harvey, S. C. The quantitative determination of the chlorides in the urine. *Arch. Int. Med.*, 6: 12, 1910.
15. Van Slyke, D. D. The determination of chlorides in blood and tissues. *J. Biol. Chem.*, 58: 523, 1923.
16. Talbott, J. H. and Coombs, F. S. Metabolic studies on patients with gout. *J. A. M. A.*, 110: 1977, 1938.
17. Newburgh, L. H. Energy metabolism in obese patients. *Bull. New York Acad. Med.*, 24: 227, 1948.
18. Levin, M. H., Adams, W. S., Beck, W. S., Goldman, R. and Bassett, S. H. Prolonged treatment of a case of periarteritis nodosa with ACTH: the effective dose as measured by metabolic balances. *J. Clin. Endocrinol.*, 11: 375, 1951.
19. Sayers, G., Burns, T. W., Tyler, F. H., Jager, B. V., Schwartz, T. B., Smith, E. L., Samuels, L. T. and Davenport, H. W. Metabolic actions and fate of intravenously administered adrenocorticotropic hormone in man. *J. Clin. Endocrinol.*, 9: 593, 1949.
20. Mason, H. L., Power, M. H., Rynearson, E. H., Ciaramelli, L. C., Li, C. H. and Evans, H. M. Results of administration of anterior pituitary adrenocorticotropic hormone to a normal human subject. *J. Clin. Endocrinol.*, 8: 1, 1948.
21. Price, N. L. Gout following salyrgan diuresis. *Lancet*, 1: 22, 1939.

Review

Correlations of Structure and Function and Mechanisms of Recovery in Acute Tubular Necrosis*

JEAN OLIVER, M.D.

Brooklyn, New York

THE problems that I wish to discuss are concerned with questions of epistemologic nosology; what constitutes a legitimate entity in the field of renal disease; how can such entities best be established; what are the causal relationships that bind them together; in general, what processes of reasoning, observation and experiment can we most usefully bring to bear on the involved entanglements of pathogenesis in matters renal? I shall not attempt to discuss such recondite considerations but I do intend to illustrate their importance by means of specific example.

Similar questions confronted William Gerhard in the early 1800's when he faced and solved such problems as distinguishing typhus from typhoid or of establishing the relation of tuberculous meningitis to pulmonary phthisis. It is true that in the field of infectious disease such difficulties have today been resolved or, as the philosophically minded might somewhat reluctantly think, brushed aside by the introduction of a strict etiologic basis for the entity; "tuberculosis" is now whatever happens when Mycobacterium tuberculosis is at work and we worry no more about the structural aspects of tubercle and caseation, of phthisis and scirrhus. But as Gerhard had to do things the hard and slow way, just so are we pathologists and clinicians still doomed to Sisyphean labors in our classifications of renal disease; no sooner is the final stone of our theoretic construction in place but it rolls back upon us.

The collapse is, however, seldom complete; some part of the imposing edifice we have momentarily admired remains to encourage another attempt. That our labor is not wasted and that our method is sound we can believe from what Gerhard wrought with the use of those ancient tools, the correlation of structural and functional change which had been handed down to him through Morgagni from still earlier times. As he then proved, typhoid is not typhus, even if the current distinction is not much concerned with the structural landmarks of intestinal ulcer and swollen mesenteric gland.

To get to our immediate point: it was about thirty years after its first recognition that Dr. Baldwin Lucké[1] pointed out common structural and functional characteristics in a seemingly heterogenous group of clinical conditions in which sudden failure of renal activity was an obvious common denominator. Being a pathologist, he quite naturally approached the problem from its structural aspect and established the entity on the basis of a structural change. That further investigations brought out certain additional minutiae and led to what are sometimes tolerantly called "semantic difficulties" is of no great importance. However, very real difficulties did appear when the functionalists in their survey of the problem came to their conclusions, for as Dr. Homer Smith[2] summed matters up, it was the functional phenomenon of "acute renal failure" with its myriad contrasting dynamic mechanisms that was the unifying key to the solution of the nosologic puzzle. The man in the middle, in particular the clinician, was therefore left with an "entity" that in its one aspect was a complex of diverse functional disturbances and in the other a restricted structural lesion. The very existence

* From the Department of Pathology, State University of New York, Medical Center at New York City. This work was supported by the Life Insurance Medical Research Fund and the New York Heart Association. Address before the Philadelphia Pathological Society, November 13, 1952 on the award of the William Wood Gerhard Medal.

of such an "entity," much less an understanding of its causal relationships, seemed incredible.

Now all of us, as pathologists, must have felt certain that this pathogenetic dilemma could in the end only be resolved by the same means that had proved so effective in the hands of

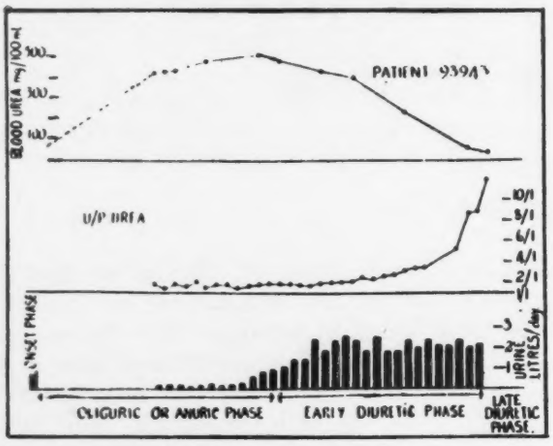


FIG. 1. Functional data on patient suffering from acute tubular necrosis, illustrating the different phases.*

Gerhard, namely, by the correlation of the structural and functional aspects of the situation.[‡] Difficulties obviously arose from the fact that in the present day, as contrasted to Gerhard's time, no one investigator could have a grasp of current methods of observation in both fields adequate to a solution of the problem. What I therefore wish to present is a description of a correlative investigation that might be said to have operated spontaneously from the efforts of independent investigators. I refer to the work of Dr. G. M. Bull and his group[3] studying the functional problem in London and that of the members of the group with which I am associated in Brooklyn who were concerned with its structural aspect.†[4]

The first of the successful correlations between the two investigations appears from the fact that Dr. Bull and his group were able to illustrate the various specific functional disturbances with which they were concerned by drawing their examples indiscriminately from the large group in which acute renal failure had complicated a great variety of clinical situations, such as, "ingested poisons, mismatched blood transfusions, abortion, concealed accidental hemorrhage, "shock," surgical operations, etc."[3] The same was true of our choice of the illustrations of the structural lesions. This conformity, which includes the consideration of a remarkably varied series of complex functional and structural disturbances, would seem to establish without question not only the theoretic but also the practical value of considering an entity which seems at first glance to be a heterogenous diversity.

Let us look now at the general aspect and course of the disturbances of renal activity as the functionalists saw them. Figure 1 shows a typical example, beginning with a period of oliguria and rising blood urea concentration which is followed by a diuretic phase and a return of the blood urea content to normal, with ultimate recovery.

A detailed analysis of the data in the oliguric period showed disturbances which were interpreted as evidence of decreased renal blood flow and a consequent reduction of glomerular filtration. (Fig. 2.) Concomitant with these alterations were indications of profound and long-lasting tubular dysfunction as manifested by: (1) a loss in the ability of the tubules to concentrate waste products as indicated by the concentration ratio (U/P) of urea and creatinine (Fig. 3); (2) a loss of the ability of the tubules to conserve ions (Fig. 4); (3) an inability of the tubules to extract PAH from the blood (Fig. 5); and (4) a reduction in the ability of the tubules to absorb glucose. In this last regard it was found that TmG might be reduced to as low as one-third of its normal figure but in only one

* Figures 1 to 5 and 10 are reprinted from *Clin. Sc.*, 9: 379, 1950.[3]

† The problem of what to call the "entity" still remains to plague us. It is interesting that Dr. Bull, a physiologically minded clinician, preferred the anatomic term of "acute tubular necrosis" while as a morphologic pathologist I tried to shift the responsibility towards the functional side with "acute renal failure." Doubtless each is more tolerant of definitions that lie in the other's field. Neither term gives consideration to the interstitial reaction which is of considerable pathogenetic importance. The Scandinavian investigators therefore logically suggest "distal tubular nephritis" and the Russians in a veritable masterpiece of etymologically dubious ingenuity have coined the word "nephroso-nephritis." I still believe that this renal lesion occurs as an "episode" in many diverse clinical situations: rather than saying "an episode caused by renal ischemia and resulting in ischuria" the adjective "ischemuric," if harsh, is short. But I have been shocked to hear the adjective made a noun with the result that a new purely metaphysical "entity" has been born in the term "ischemuria"! Since most of our clinical friends seem more comfortable with an anatomic term, and this is a great compliment to us pathologists, I intend to follow Dr. Bull's suggestion whenever a demand is made on me for a straightforward pathologic diagnosis.

case was the failure to absorb sugar so extreme as to result in glycosuria.

The general reduction in all tubular functions continued into the diuretic phase, with a gradual return towards normal in a recovery period extending over months. We shall return to a further consideration of these latter stages when the structural lesions are presented for correlation. For the present it is of interest that all the tubular dysfunctions noted are localized by current physiologic interpretations in the proximal convolution. Of the localization of one of these, the lessening of the ability to absorb glucose, we can be reasonably certain; the micropuncture studies in mammals of Walker, Bott, Oliver and MacDowell[5] have shown that this process is completed in the proximal convolution. Lack of evidence of a functional lesion at a lower level does not, of course, preclude the possibility that this portion of the nephron is not also damaged. Functional disturbances in this

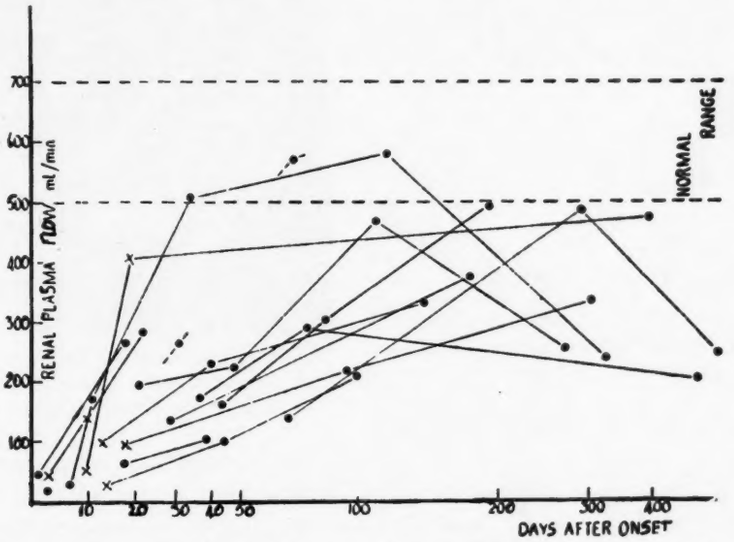


FIG. 2. The renal plasma flow in patients suffering from acute tubular necrosis.

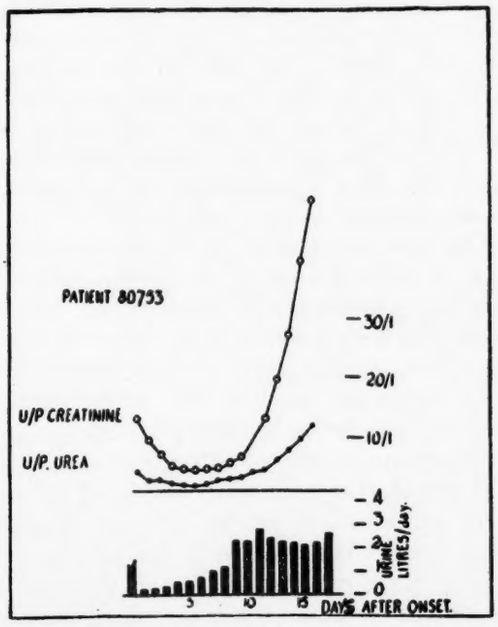


FIG. 3. The inability of the kidney to concentrate urea and creatinine in the urine in acute tubular necrosis.

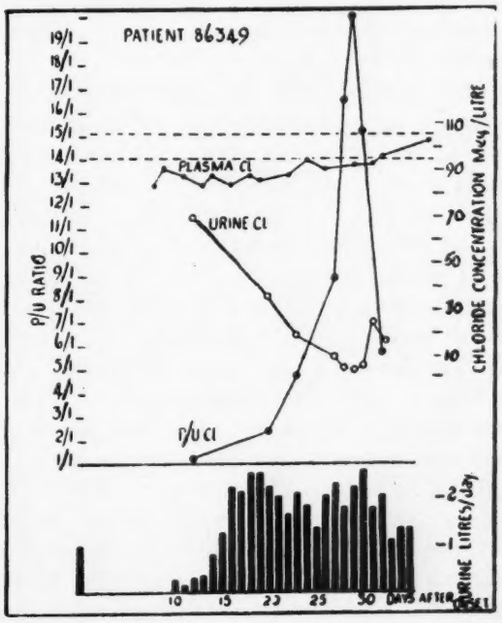


FIG. 4. The inability of the kidney to conserve chloride in acute tubular necrosis.

region are notoriously difficult to demonstrate under any conditions, much less when they are masked by disturbances in the proximal tubule. It would seem fair to state therefore that, from the functional viewpoint, the data so far presented indicate the importance of disturbances

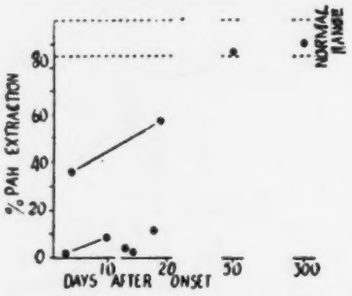


FIG. 5. The percentage of renal extraction of PAH in patients suffering from acute tubular necrosis.

high in the nephron rather than in its lower reaches.

Finally, in their discussion and summary Dr. Bull and his associates venture into the problem of pathogenic theory; in their words, "We would suggest that there are two types of acute tubular necrosis, one resulting from poisoning of the kidney cells and the other from very severe renal ischemia."[3]

This then is what the functionalists found going on in the kidney: what did the morphologists see in the way of structural change in the nephrons that can serve for correlation?

In the case of the glomerular lesion, the picture in the oliguric period is of an intact tuft, its capillaries collapsed and bloodless. (Fig. 6.) That its tissues are not entirely normal is suggested by the occasional presence of protein in the capsular space, but there seems little reason to believe that, the capillary blood flow reestablished, it could not filter adequately and, from the evidence of its increased permeability, perhaps excessively. The structural aspect of the glomerular lesion agrees quite exactly therefore with the conclusion derived from the functional examination that a simple reduction in renal blood flow and consequent reduced filtration is the major disturbance during the oliguric phase.

In his assessment of the structural condition of the tubule I presume it will be generally admitted that if the morphologist wishes to express a valid opinion he should at least look at the object concerned and this can only be done if he examines it in its complete continuity.

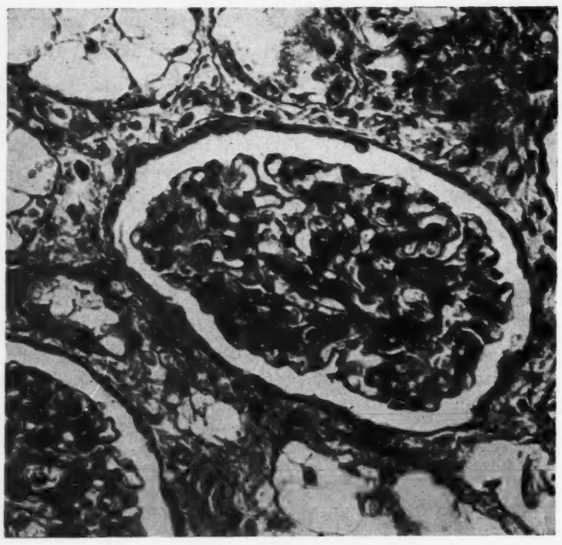


FIG. 6. The intact but collapsed ischemic glomerular tuft in the oliguric phase of acute tubular necrosis. Di-ethylene glycol poisoning, twelve-day.

The method of microdissection affords the means to this end and by its use it is evident that extensive tubular damage is the dominant lesion among all the structural changes found in the kidney. It is moreover quite clear in the dissected material that all parts of the tubule of the nephron from glomerulus to collecting duct are affected by destructive processes. In particular is the proximal convolution involved (Fig. 7), a point in close conformity with Dr. Bull's findings that the functional disturbances are those which concern mechanisms of proximal convolution activity.

The most remarkable of the positive correlations between the results of the functional and structural examination is revealed, however, when it is discovered that there are two quite distinctive tubular lesions in the same kidney and, at times, even in the same nephron. (Fig. 8.) One lesion is confined to the proximal convolution: it presents all the characteristics that pathologists have long considered the result of the action of a poison on epithelial cells; since the proximal convolution is the principal absorbing segment of the nephron, it is not surprising that it shows the toxic effect, nor, since poisons reach the nephrons by a blood stream which is evenly distributed, that all proximal convolutions are involved.

The other lesion can be described as a disruption of the continuity of the tubule that includes dissolution of its basement membrane; this tubulorhexis may be limited to a short

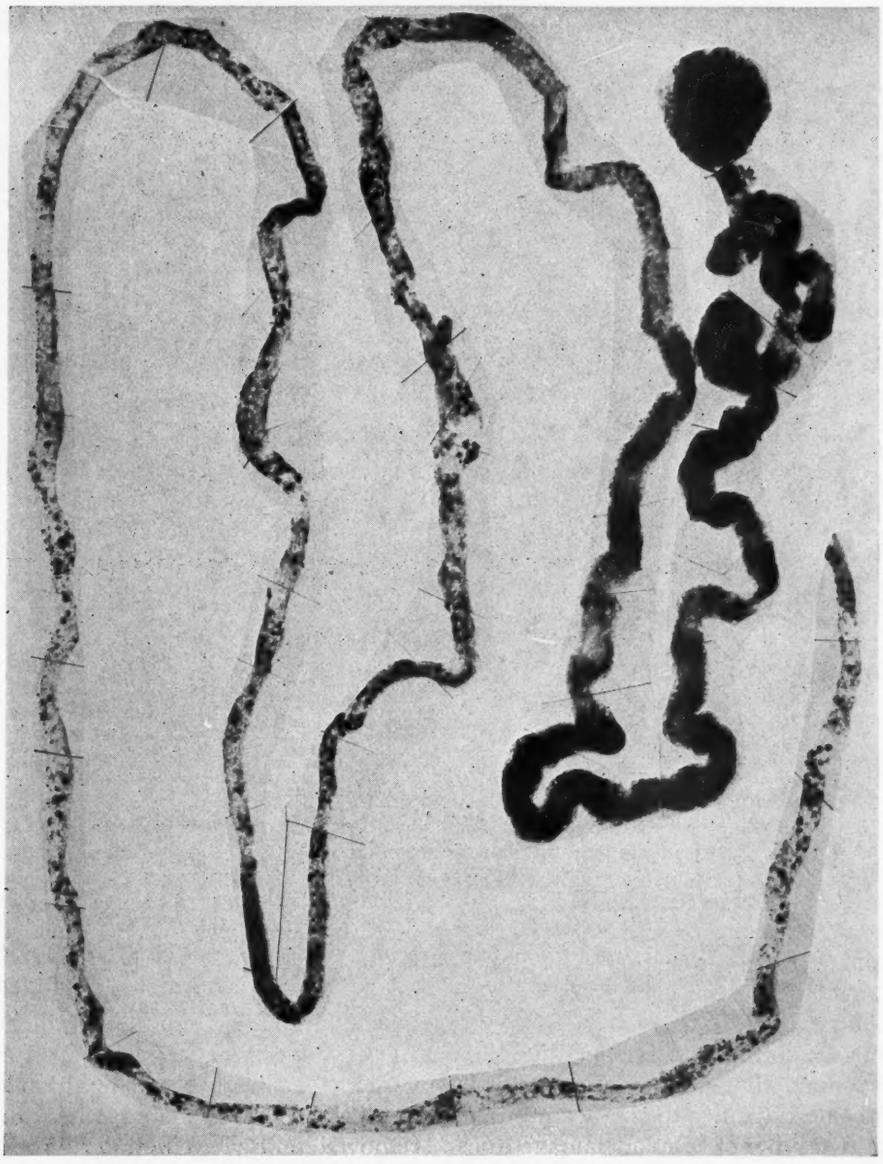


FIG. 7. Complete proximal convolution from acute tubular necrosis following fatal burns. Death on ninth day. In its first loop (right), the tubule is fairly well preserved; from there on extensive tubulorhexic damage.

segment or involve long stretches. It is clearly the lesion described by Dunn, Gillespie and Niven[6] in histologic sections as occurring in the distal convolution of the "crush kidney." When the continuity of the dissected nephron was available for examination, however, this alteration was found not to be limited to any particular segment; it occurred with a singular randomness of distribution from the origin of the tubule in the proximal convolution to its end in the collecting duct. Furthermore, not every nephron was affected; many had escaped although all of the proximal convolutions in the same kidney might show the other type of nephrotoxic lesion.

Here then are two very different sorts of tubular damage to fit the two etiologic factors of "renal poisoning" and "severe ischemia" that Dr. Bull and his coworkers had postulated from their functional findings. Is it merely a coincidence that the morphologist finds two lesions where the deduction of the functionalist had indicated a dual causation? I think that pathologists would be willing, on the basis of the structural characteristics of the damage alone, to consider the matter settled. One lesion

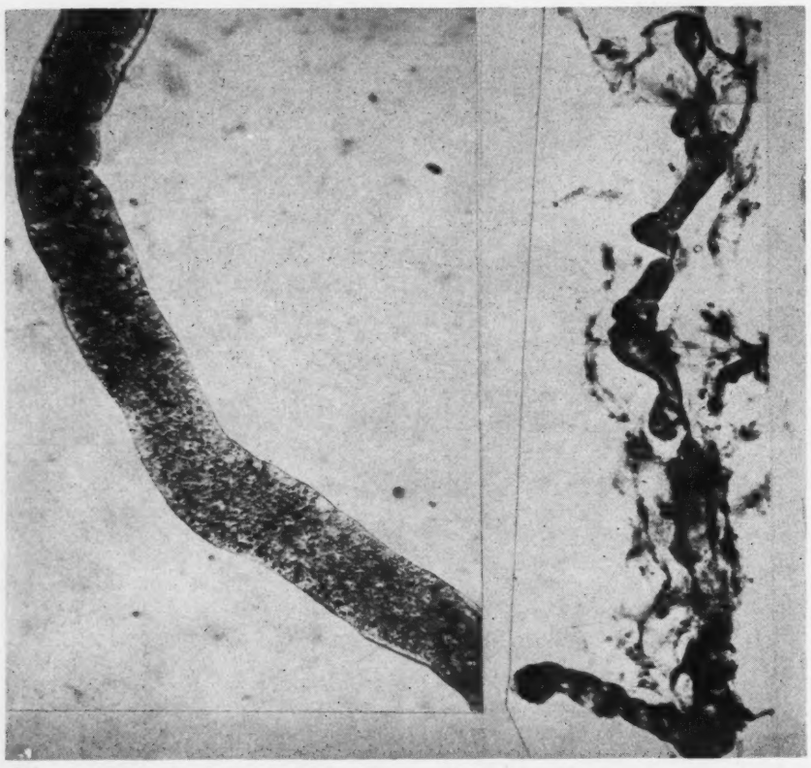


FIG. 8. The two tubular lesions of acute tubular necrosis. Left, nephrotoxic damage due to sublimate poisoning (dog, death on sixth day). Note disintegration of epithelium with intact basement membrane. Right, disruptive tubulorhexic damage due to sulfonamide (human, death on tenth day).

appears definitely in both its nature and location a toxic effect; for the other, particularly in the randomness of its distribution, it is difficult to conceive of any other cause except an irregularity of vascular supply.

In acute renal failure there is one example, sublimate poisoning, that might be considered as presenting some difficulty to the assumption that there are two types of tubular damage due to two causes, for *a priori* simple toxic action would seem an adequate explanation of the renal lesion. It is true that Dr. Bull and others have shown by functional technics that a reduction in renal blood flow occurs in the severe clinical forms of this intoxication, but there is also functional evidence that suggests, if it does not prove, that there is no reduction of blood flow when this and other analogous poisons are studied under experimental conditions.[3] Moreover, the earlier descriptions of the structural lesion[7] imply, if they do not explicitly state, that the renal lesion is a simple necrosis of the proximal convolution.

Toward the clarification of these discrepancies the pathologist can make what might be called a dynamically morphologic observation, for the distribution of the blood flow through the kidney can now be seen by means of the Schlegel technic[8] in which a fluorescent dye is injected into the circulation of the living animal. In this experiment the glomeruli and terminal vessels that were receiving blood during life are brightly illuminated when the kidney is removed and viewed under Wood's light. An examination by this procedure of kidneys damaged by various nephrotoxic agents showed that in all cases an irregular, patchy ischemia had developed. (Fig. 9.) In the dissected nephrons of these kidneys the random tubulorhexic lesions were found, as well as the ubiquitous toxic damage to the proximal convolutions.

The demonstration of a patchy, renal ischemia by morphologic methods under conditions where functional procedures have shown little or no reduction in total renal blood is of considerable interest, for it indicates that the latter measurement may leave undisclosed the intimate circulatory relations within the kidney and it is on these that not only the maintenance of tissue integrity but also the pattern of the

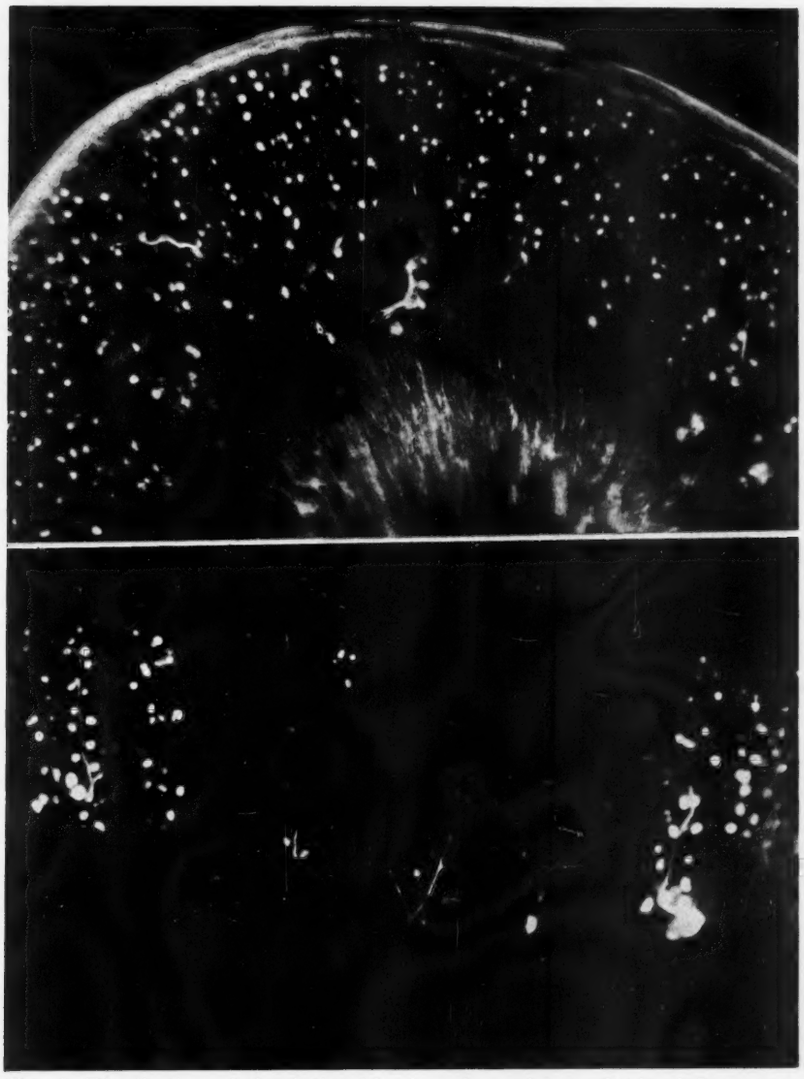


FIG. 9. Distribution of circulating blood as shown by the Schlegel fluorescent technic. Above, the even cortical pattern of the normal rabbit kidney. Below, the patchy cortical ischemia on first day of sublimate poisoning. The nephrons of this kidney showed extensive tubulorhexic ischemic damage.

functional activity of the nephrons depend. In this regard it might be stated that there was no evidence in the visualized preparations of a shunting of blood from cortex to medulla; here too there is conformity with Dr. Bull's functional observation that the renal arteriovenous oxygen differences were increased when the renal blood flow was low.

A final correlation, or perhaps one should say an explanation on a structural basis of what appeared to be a minor discrepancy in the functional evidences of tubular dysfunction, may be added. Dr. Bull and his coworkers are somewhat disturbed by the fact that in cases in which severe impairment of tubular ability to concentrate urea and creatinine, to conserve sodium chloride and to extract PAH were noted, the ability to absorb glucose was markedly less affected. It will be recalled that in one case TmG was indeed reduced to one-third but in only one instance was there frank glycosuria.

The morphologist who studies the entire proximal convolution in a dissected nephron is not greatly surprised by this apparent paradox of persistence in glucose absorption. He knows from the studies of Walker, Bott, MacDowell and myself[5] that in the mammalian nephron sugar absorption is, for all practical purposes, completed in the first half of the proximal convolution. This portion commonly escapes the

maximum damage that is produced by most toxic substances, so that even in the severely affected proximal convolution there is, at least from the morphologist's viewpoint, a considerable Tm remaining. This is also true when a considerable part of the proximal convolution has been destroyed by tubulorhexic damage. (Figs. 7, 21.)

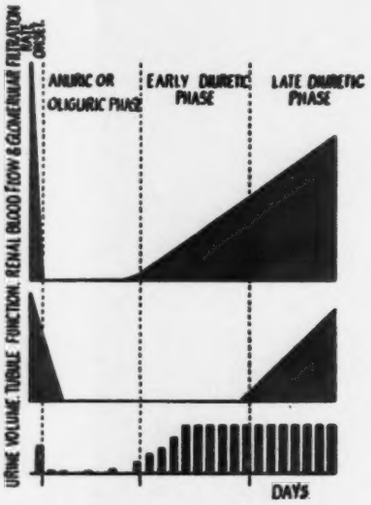


FIG. 10. The over-all pattern of disturbed renal function in acute tubular necrosis.

So much for the correlation of the structural and functional aspects of the lesions of acute renal failure during the oliguria. If death does not intervene, there now follows a protracted period of recovery. This is characterized functionally by the appearance of a diuresis which Dr. Bull and his coworkers divide into an early and late phase, the first being distinguished by a gross outpouring in the urine of essential electrolytes, a loss which is gradually corrected as restitution of tubular activity occurs in the late phase. The functional investigators do not say much as to the mechanisms of the increased output of water, although it is apparent from their schematic Figure 10 that as recovery occurs two factors might operate to produce a diuresis; first, the return of an ever-increasing renal blood flow with immediately increased filtration concomitant with persisting tubular dysfunction which includes a decrease in the absorption of water. A difference in time relations in the recovery of glomerular and tubular activity could thus be an important factor in the onset of diuresis.*

What the morphologist sees at this critical period when oliguria changes to diuresis is helpful to an understanding of the situation for

* The "cause" of variation in the output of water, whether taking the form of anuria, oliguria or diuresis, comprises a most elaborate constellation of positive and negative factors and, as we have just indicated, time relations as well. A consideration of these complexities would lead us beyond reasonable limits in this discussion but has been attempted in another place.[4]

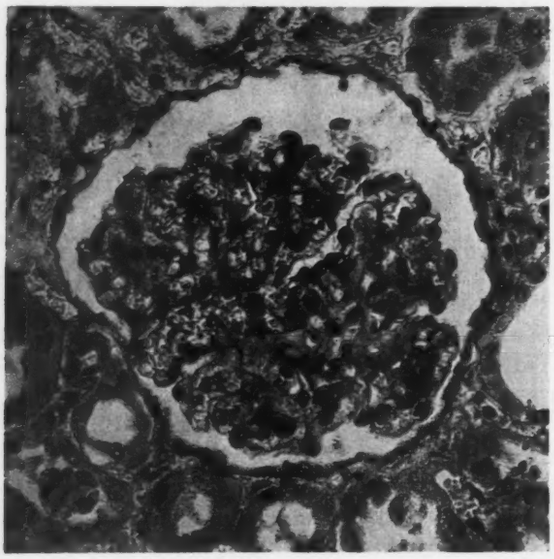


FIG. 11. Distended, blood-filled glomerular tuft of essentially normal structure from diuretic phase (115 cc./24 hours) of acute tubular necrosis following di-ethylene glycol poisoning with death on twenty-third day.

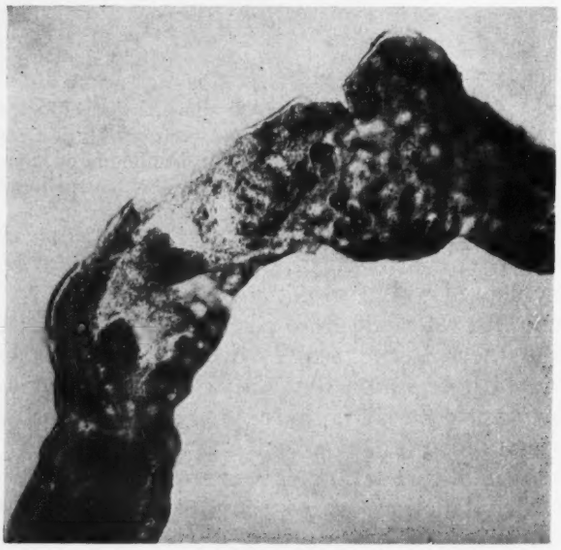


FIG. 12. Tubulorhexic lesion in distal convolution due to sulfonamide poisoning; death on fourth day. Note masses of regenerating dark-stained epithelium proliferating at random due to disruption of basement membrane.

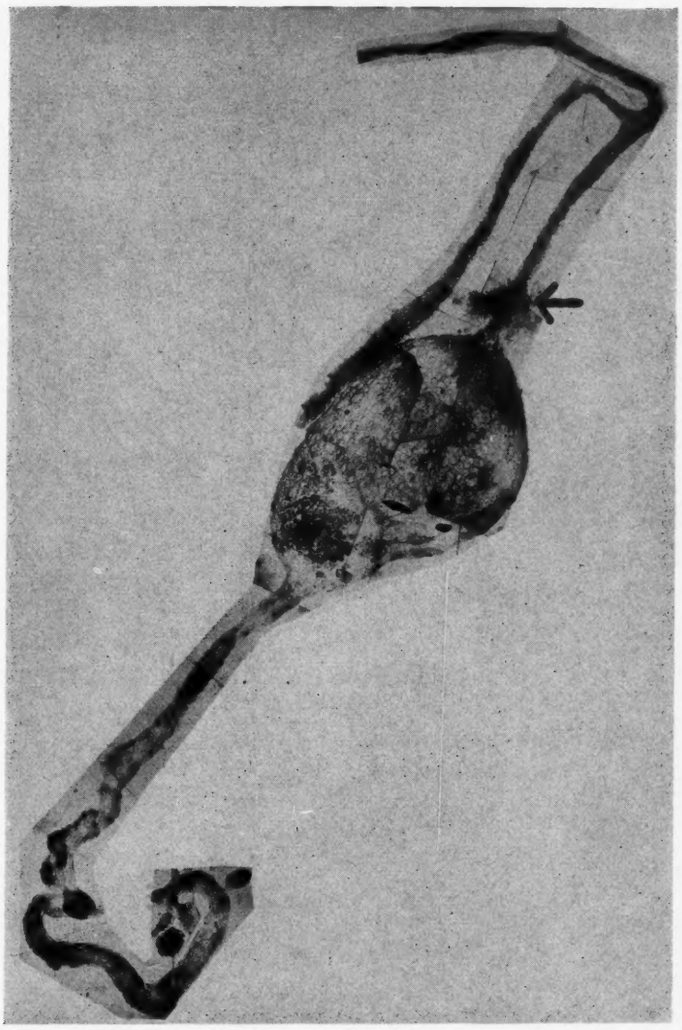


FIG. 13. Connecting tubule with cystic dilatation proximal to a point of occlusion (arrow); sublimate poisoning with death on twenty-ninth day.

it confirms the suggestion that time factors determine not only the course but also the nature of the functional aspects of recovery. You will remember the illustration of the glomerulus in the period of oliguria, its tuft structurally intact but bloodless with some evidence that its membranes were more permeable. (Fig. 6.) No lapse of time for reparative processes is therefore needed for restitution of its function; the simple return of renal blood flow distends its capillaries and results in the usual, or perhaps increased, filtration. (Fig. 11.)

In contrast to the immediate recovery of glomerular activity re-establishment of tubular function is long delayed, for the data of Dr. Bull and his coworkers show irregularities in the balance of tubular mechanisms over a period of weeks and even months. We shall now consider the structural reasons for this difference.

From the widespread damage you have seen in my earlier illustrations it is apparent what an extensive job of repair is required in the tubules of the nephrons if they are again to function adequately. Moreover the difficulty of accomplishing this end is greatly complicated by the fact that the repair must be all or none; a tube that is completely relined except for one break in its wall or that is occluded at a single point in its lumen may be useless as an excretory organ no matter how much epithelial regeneration has occurred. It is nephron reconstitution, therefore, that counts, not epithelial regeneration, and this information can be obtained only by looking at complete nephrons.

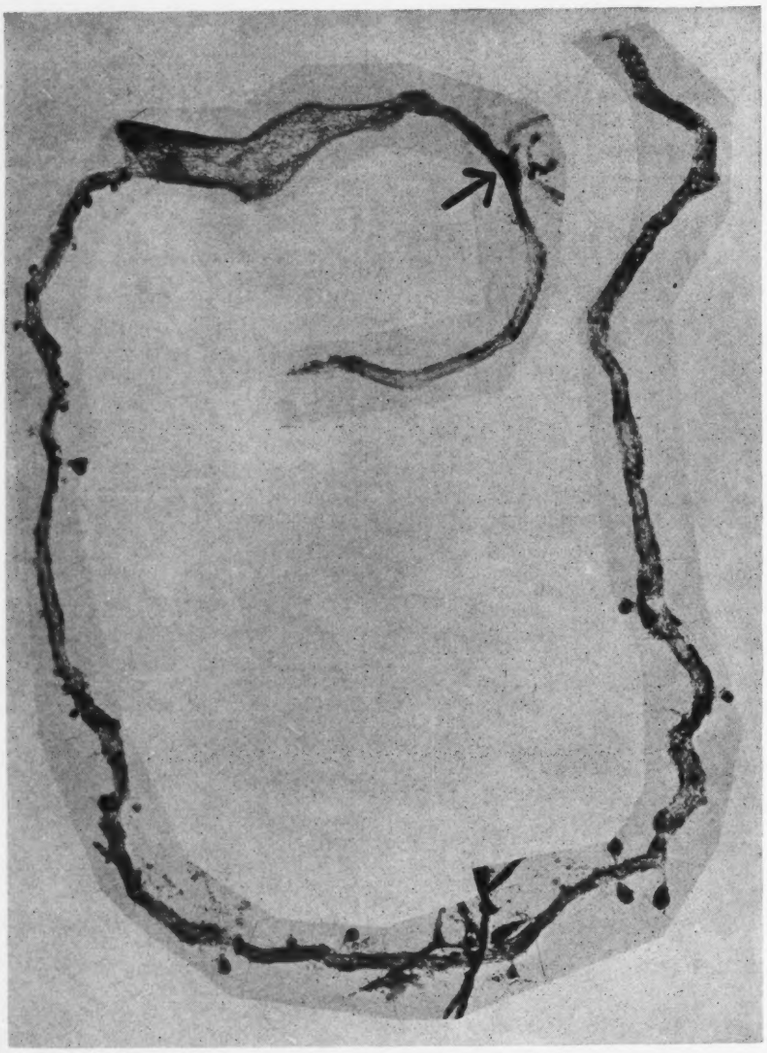


FIG. 14. Permanent atresia, a result of an earlier attack of paroxysmal hemoglobinuria, with deformity of distal convolution. Other nephrons from this kidney were reduced to fragmented remnants.

If one considers again the structural characteristics of the two types of tubular damage (Fig. 8) it is also evident that the problem of return to structural integrity is very different in the two instances. In the case of the nephrotoxic lesion we have to deal with what appears to be a relatively simple requirement; a new inner tube of epithelium is needed to cover the still intact basement membrane. In the tubulorhexic disruption a patch of two tissues, epithelial and mesenchymal, must be organized to reform the tubule wall.

Let us consider the latter, more difficult situation first. A glance at a few illustrations of its processes shows that there is no lack of regenerating potency in the epithelial cells at the point of disruption (Figs. 8, 12); the difficulty comes from the orientation of their proliferating masses to bridge the gap in the tubule wall and in the replacement of the basement membrane that supports the tubule. If the disruption is limited, doubtless this total repair is possible; if it is extensive, unlikely.

It seems certain therefore that many of the nephrons containing extensive tubulorhexic disruptions never again became functioning units. Frequently an atresia persists and in spite of complete relining the tubule proximal to the point of imperfect repair undergoes dilatation and later atrophy. This we were able to see not only during the acute manifestations of the renal lesion (Fig. 13) but also in a case in which

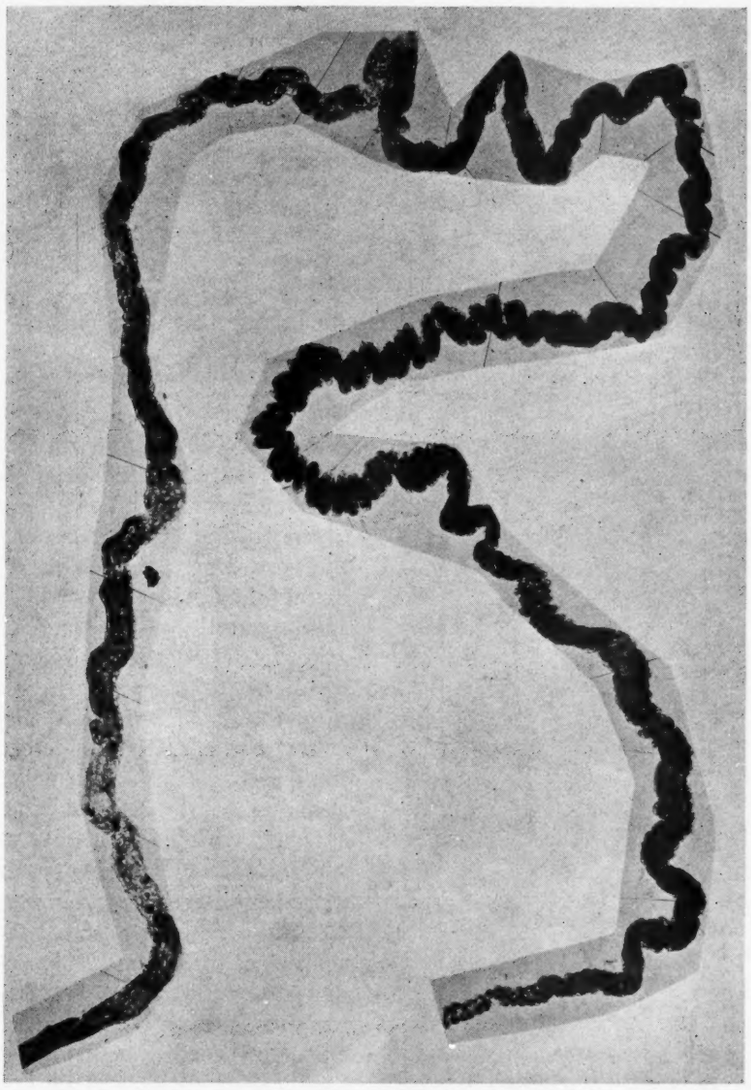


FIG. 15. Portion of a complete proximal convolution from kidney after sublimate poisoning; death on fourteenth day. Extensive nephrotic damage on left; on right, hyperplastic proliferation of dark-stained living cells with production of tubular kinking.

repeated attacks of paroxysmal hemoglobinuria had left their traces of earlier abnormal repair in the form of malformed nephrons of dubious functional value. (Fig. 14.)

The loss of even a considerable number of nephrons is perhaps not too serious a matter in an organ such as the kidney which has a large normal reserve. Since the tubulorhexic lesions are from their pathogenic origin random, many nephrons are not involved, in contrast to the universality of whatever nephrotoxic lesion may be present. Furthermore, there are fundamental biologic mechanisms of compensation that can operate when the margin of safety is approached, namely, hypertrophy and hyperplasia of the cellular elements that have escaped damage. Figure 15 shows a portion of a proximal convolution, in part damaged and in part lined with living cells; the proliferation of the latter has thrown the tubule into a series of irregular thickened coils that add, to use the functionalist's term in its literal sense, a considerable amount of Tm to the nephron.

From the structural viewpoint it would therefore seem that permanent damage is done to the kidney even if the totality of renal activity is not greatly affected. Here, too, the correlation with the functional findings is remarkably close; Dr.

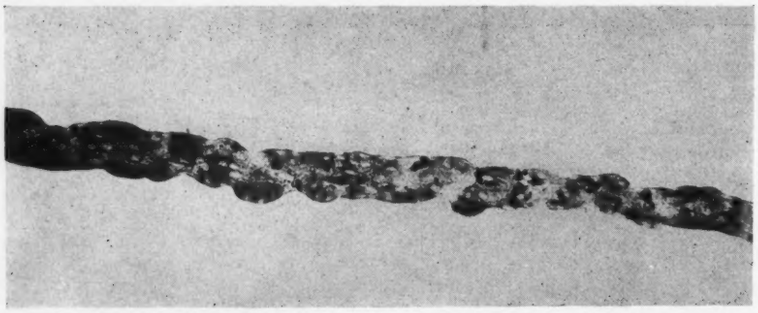


FIG. 16. Extension of regenerating epithelial cells along basement membrane from the persisting cells (left) at the edge of the epithelial defect; sublimate poisoning; death on fourteenth day.

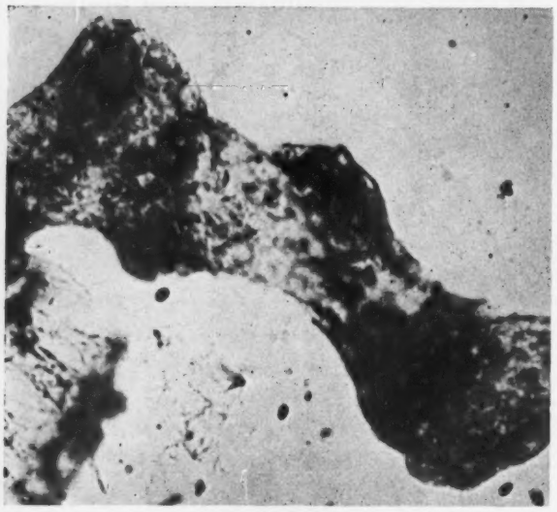


FIG. 17. Proliferation of regenerating epithelium from islands of surviving cells scattered on the intact basement membrane; sublimate poisoning; death on fourteenth day.

K. G. Lowe,[9] reporting an interim follow-up on fourteen of the original cases studied by Dr. Bull's group, finds that although "good clinical recovery was the rule," renal function as tested by various clearance methods still "remained below the lower limits of normal" after a three-year period.

There is no reason to believe, speaking again from the structural aspect of the lesion, that the damage is progressive, as is the case in chronic inflammatory renal disease. Such an individual simply has fewer nephrons to spare. However, in light of the fact that renal ischemia is an accompaniment of so many clinical disturbances, the possibility presents itself that repeated and undetected destruction of nephrons might bring the renal totality down to a level of physiologic hazard or even difficulty; but this is speculation for future attention.

As I have stated, the repair of the nephrotoxic lesion would appear to present at least lesser mechanical difficulties. The basement membrane is intact to serve as a guiding surface for the proliferating cells and these, with the exuberance that was noted long ago by Weigert, spread rapidly along the tubule. The new cells arise from those that have escaped the toxic insult, so that we see them extending inward over the bare basement membrane from the edges of the epithelial defect. (Fig. 16.) Since the length of damaged tubule may be considerable, as in the case of the epithelization of external wounds, it would seem unlikely that spread from the periphery, in this case the two extreme ends of the damaged segment, could cover the entire surface. Fortunately there are islands of persisting cells scattered along the denuded tubule, and from these, analogous to the proliferation that springs from the scattered epithelial grafts of the surgeon, the defect is finally covered. (Fig. 17.)

As we have described the process so far, no particular difficulties have been encountered. As pathologists we would perhaps anticipate trouble, for we are accustomed to see reparative processes that seem ideally suited to the local situation go awry with disastrous results to the organism as a whole. There are in fact two weak points in the mechanism of nephrotoxic repair that prejudice the recovery of the patient.

The first of these, to which we have already alluded, is the excessive exuberance of the regenerative proliferation, the Weigert phenomenon; the other, the very considerable time that is required for essential maturation of the regenerated cells to a structural constitution compatible with normal function. It is one thing to plug holes and reline tubes and quite another to restore intracellular mechanisms as exqui-

sitely delicate as those that operate in the epithelium of the proximal convolution, and it is in this vitally functioning portion of the nephron that the nephrotoxic lesions occur.

For examination of these intimate cellular details it becomes necessary to turn to the experimental animal, first because the structural changes must be viewed at determinate intervals during the period of recovery and secondly because the tissues must be fixed immediately for proper cytologic examination. Fortunately, we shall be dealing with an identity of etiology in our experiments since rats can be poisoned with corrosive sublimate; there of course remains the weaker aspect of all experimental procedures, in that we shall be seeing how a rat, not a man, behaves, so that it is well to remember what is commonly overlooked, namely, that in the last analysis we shall be arguing from analogy not identity.

A series of rats was given the same dose of corrosive sublimate in such amount that the majority of them survived after a period of oliguria in which they were very ill. During the oliguria their scanty urine contained a heavy cloud of protein and many epithelial cells and casts. In a total of forty injected animals, six died on the fourth or fifth day; the others recovered, their urinary sediment became normal and, appearing "clinically" well, they were killed at intervals up to fifty-three days. We hope at a later time to give a detailed description of the functional aspects of this experimental lesion; at present only the datum of urine

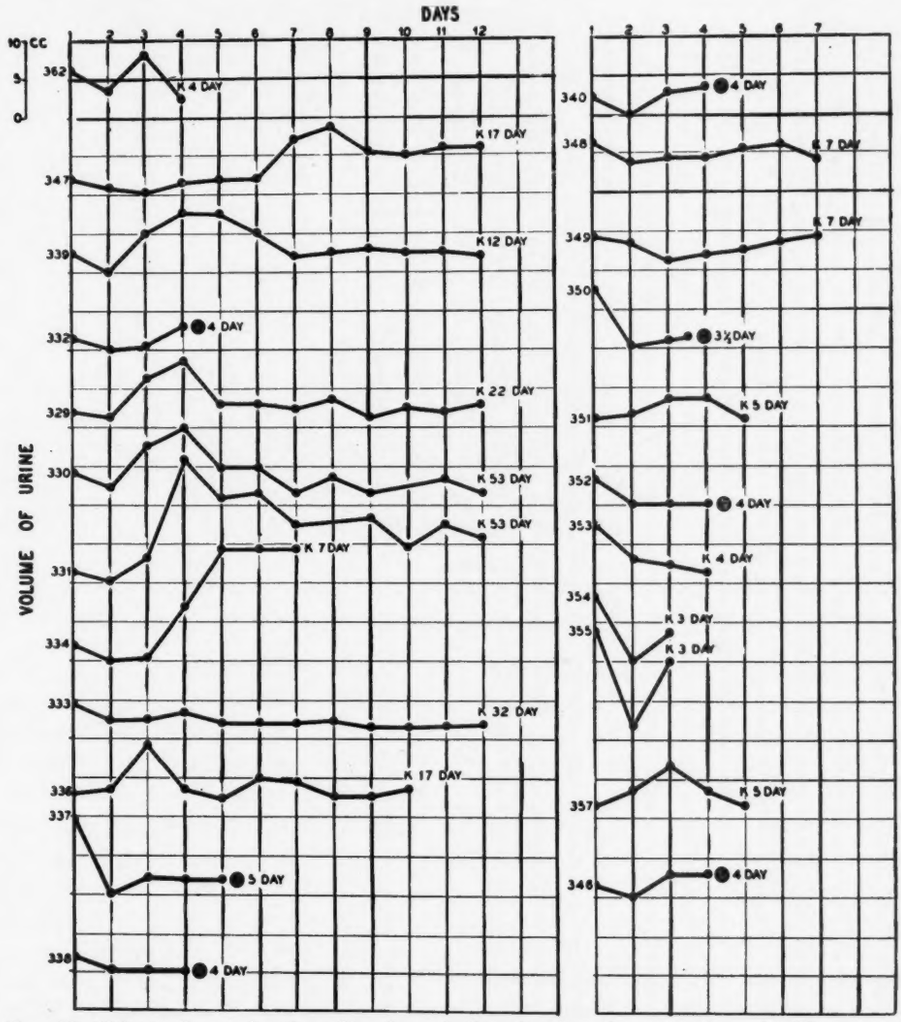


FIG. 18. Urine volume showing oliguric and diuretic phase in rats poisoned with a constant standard dosage of sublimate. Dark circles indicate death of animal; the others were killed at various times.

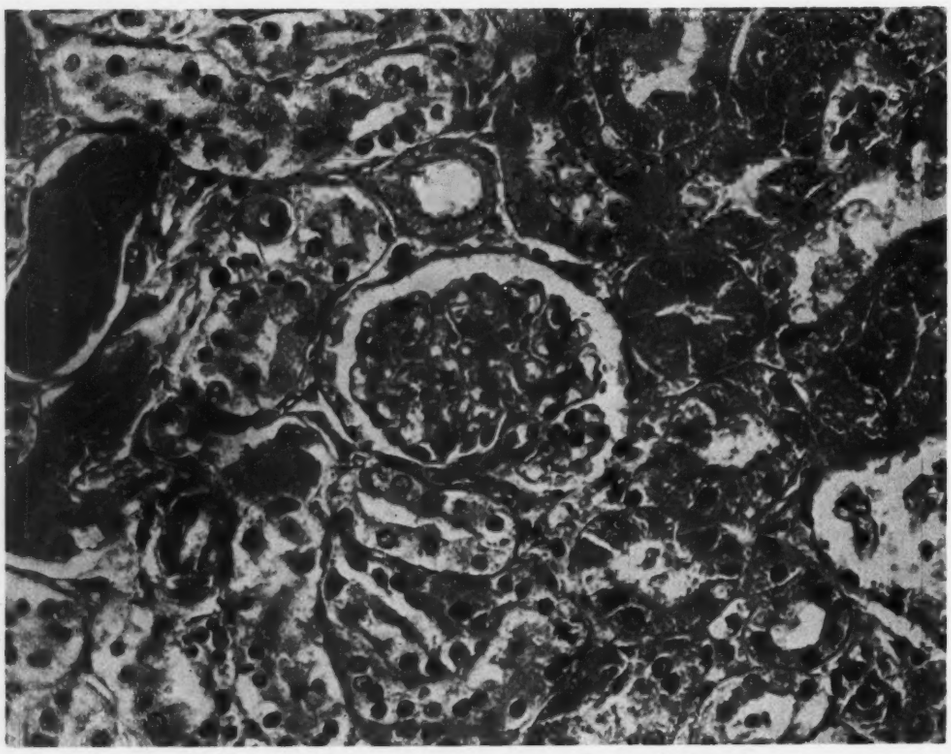


FIG. 19. Experimental renal damage in rat kidney on fourth day after standard dosage of sublimate; glomerulus, structurally intact; to right, living but damaged proximal convolutions; to left, frank tubular necrosis.

volume is available, but it at least shows that, analogous to the human cases, many of the surviving animals developed, after an oliguria, a diuresis which in some examples continued for a considerable time. (Fig. 18.)

The tubular lesions observed were chiefly those of nephrotoxic damage in the proximal convolutions; we had indeed deliberately endeavored to avoid the more severe ischemic tubulorhexic lesions, so difficult of repair, by administering the poison not only in the minimum dosage that would produce frank renal damage, but also by giving it subcutaneously in order that it would only gradually reach the kidneys.

Let us look at the structural status of the kidney of a typical animal on the fourth day after the injection, a time when the destructive lesions are at their height yet the reparative process well under way. A low power view would show the entire cortex filled with cross sections of tubules in every stage of involvement from what may be described as cloudy swelling to complete necrosis. At a higher magnification (Fig. 19) the best preserved lie about the structurally intact glomeruli and clearly represent loops of proximal convolutions; their epithelium is swollen and granular and no brush border is visible but the nuclei stain normally and the cells are apparently alive. The other cross sections are so disturbed as to defy identification, their epithelium is either dead or, if living, completely atypical, varying in its appearance from a layer of small, deeply staining cells to large, giant cell masses with vesicular nuclei.

By seven days a profound change has occurred; in the over-all view a general dilatation of what appears to be all kinds of "tubules" is evident and their sharp-cut outlines are in marked contrast to the confused pattern of the earlier stage. A higher magnification explains both appearances. (Fig. 20.) The clarity of outline is due to restitution of the normal original cytologic configuration in those proximal convolutions which had survived the early damage; their nuclei are regularly arranged and the brush border can be clearly seen. The regenerated epithelium in other cross sections is now so excessive that they no longer represent tubules but rather cords of atypical cells with no or only a rudimentary lumen. Orientation and consequent understanding of this confused picture becomes pos-

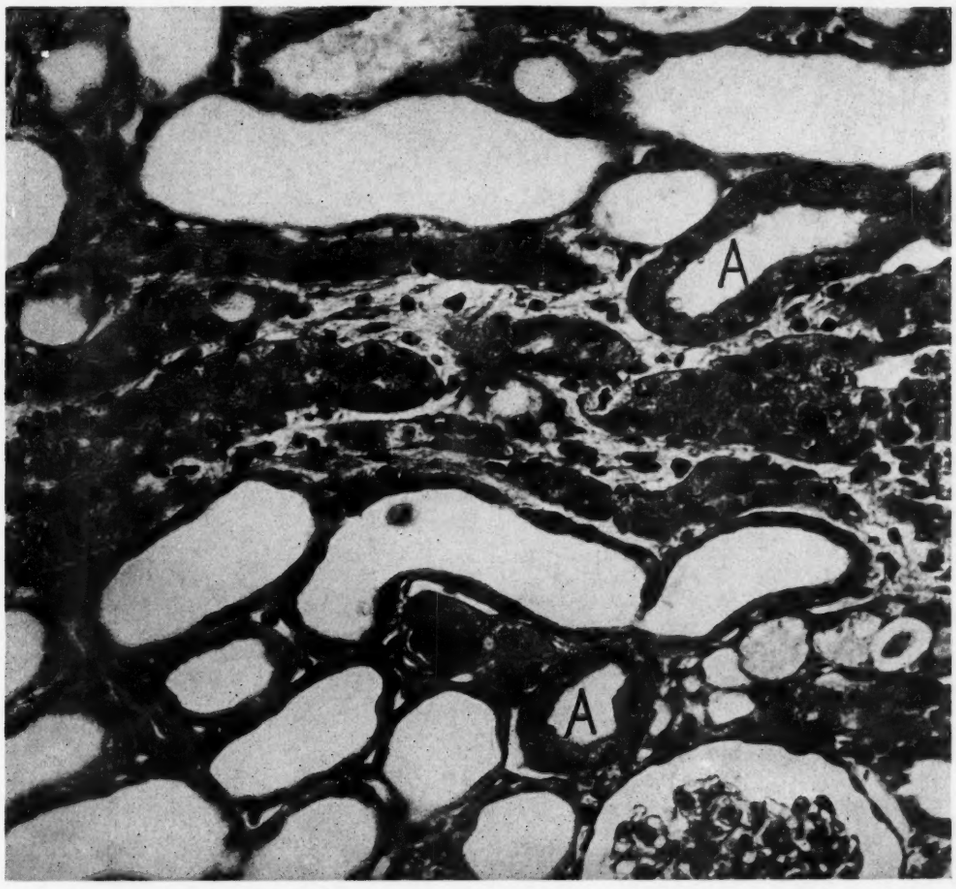


FIG. 20. Regeneration in rat kidney on seventh day. At (A) persisting proximal convolutions now showing brush border. Other "tubules" are lined with a flat immature epithelium and are dilated. Still other "tubules" consist of solid cord-like structures. Note mitotic figure.

sible when we look at a complete proximal convolution from the same kidney. (Fig. 21.) It is apparent that what has happened is the development of an atresia from excessive and irregular cellular proliferation which, along with entrapment of debris, has resulted in retrograde dilatation that involves the middle portion of the convolution. The first portion of the convolution appears remarkably well preserved and essentially normal.

Within a week or ten days the first stages of epithelial repair are completed and there now follows a prolonged period of cellular maturation. The epithelial cells rearrange themselves in the more orderly pattern of a lining membrane and lumina are re-established. As a result tubular dilatation decreases and disappears and the general picture of the renal cortex begins to assume its original appearance. And so the processes of restitution proceed. After fifty days, a long time in a rat's life, the cortical pattern appears essentially normal except for an occasional small area of tubular irregularity. Closer examination shows in these regions a cluster of tubule cross sections still lined with an atypical epithelium surrounded by other cross sections whose epithelium now presents an entirely normal and mature configuration.

Judged from the course of the structural repair as it has been seen so far in the rat's kidney, the long-continued tubular functional insufficiency that was observed in the human cases is now understandable. A correlation by analogy seems entirely proper, for those occasional human cases which survived up to as long as thirty days, when death made their kidneys available for examination, showed the same morphological type of flattened regenerating epithelium as was observed in the rat's kidney. (Fig. 22.) It would seem reasonable to assume therefore that in man the early phase of diuresis with loss of electrolyte and the other phenomena of tubular insufficiency is correlative with the structural immaturity of the regenerated epi-

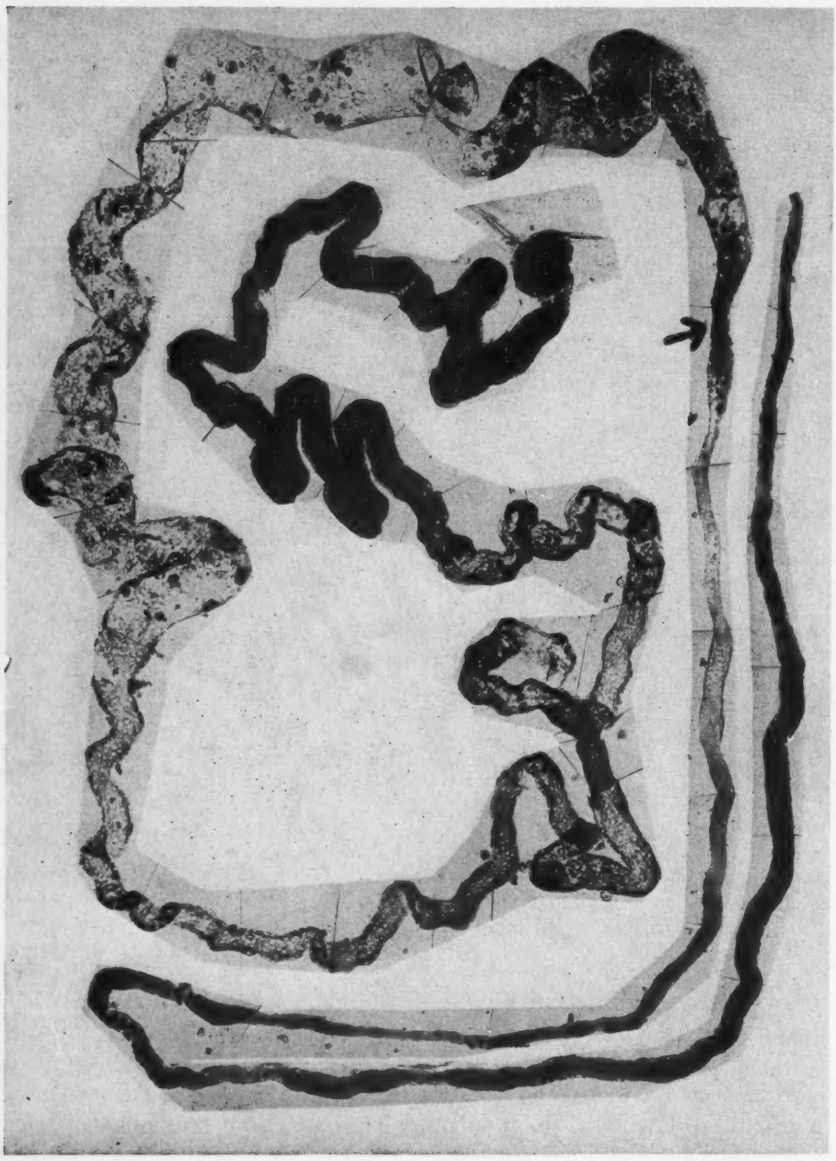


FIG. 21. A complete proximal convolution from the same kidney as in Figure 20. The first portion of the convolution is heavily stained and essentially normal. Then follows an increasingly dilated segment proximal to the atresia (arrow).

thelium which has by this time relined the damaged proximal convolutions. That the atypical appearance of this new tubular lining, in particular the flatness of its epithelium, is not the result of a generalized, simple distention of tubules by the excess fluid of the diuresis is evident from Figure 21, where it is seen that tubular distention is limited to a portion of the proximal convolution and is due to local obstruction. Moreover, it can be shown that flatness of the epithelium is the least of the cytologic characteristics by which the new cells differ from the original epithelium of the proximal convolution. The nuclei are in excess and nuclear-cytoplasmic ratio is altered. (Fig. 22.)

A more exact cytologic examination of the process of maturation of the new-formed cells confirms this further step in our correlation of structure and function. In 1916[10] I noted that the regenerating cells following uranium nitrate poisoning contained few if any of their usual mitochondrial elements, the rodlets of Heidenhain, and that this structural defect was accompanied by a functional inability to concentrate within their cytoplasm what appeared, by the

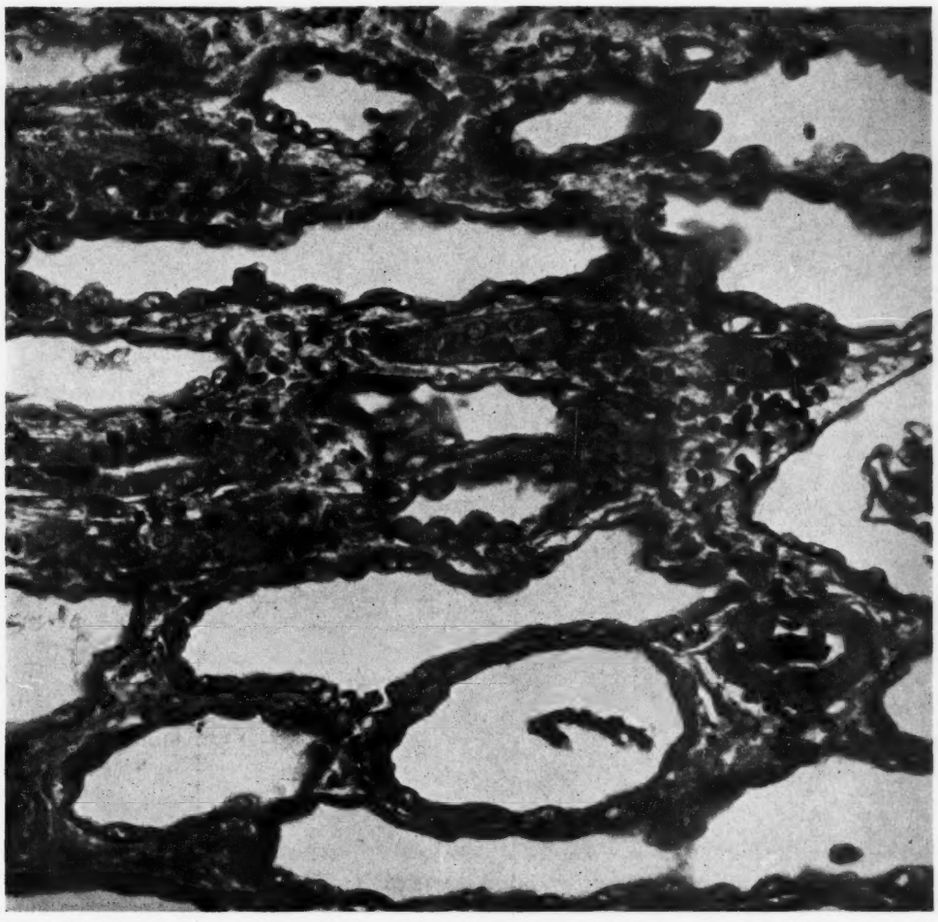


FIG. 22. Regeneration in human kidney nine days after sublimate poisoning. Note the similarity of the structural changes (flattened immature regenerated epithelium and cord-like tubules with rudimentary lumens) to that observed in the experimental rat kidney. (Fig. 20.)

then generally accepted histochemical technic, to be urea. Later[11] we found that similar mitochondria-free atypical cells in chronic canine Bright's disease were unable to absorb trypan blue from the tubule lumen.

These old observations indicate clearly enough that renal cells which have no mitochondrial organs have also lost certain of their functional abilities. We can, however, now go a step further in our structural correlation and see, I believe, the intracellular mechanism that is responsible for this loss of function.

The active transport mechanisms that operate in the renal tubule are known to depend on enzymatic activities. Recent developments in chemical technics have made possible an exact biochemical analysis of the mitochondria in tissue homogenates and it has been found that a great variety of enzymes are concentrated in these cell structures. Their occurrence in the mitochondria of the renal cells[12] has been confirmed by the use of these methods in our laboratory by Drs. Werner Straus and Norman Kretchmer. Two enzymes, alkaline phosphatase and lipase, can be demonstrated by histochemical means in tissue sections and by such procedures it has been shown that atypical renal cells of various sorts are deficient in these enzymatic activities.[13,14] No specific examination was made in these studies, however, of the mitochondrial content of the atypical cells.

If we now look at a section of the renal cortex stained for mitochondria from the fifty-day animal, which you will remember by ordinary histologic stain appeared essentially normal, we see a very considerable number of irregular islands of tubule cross sections with regenerated epithelium standing out in clear areas as a result of their mitochondrial deficiency. (Fig. 23.) At a higher magnification it is seen that in the tubules which still remain lined by an immature epithelium the cells contain none of the intra-

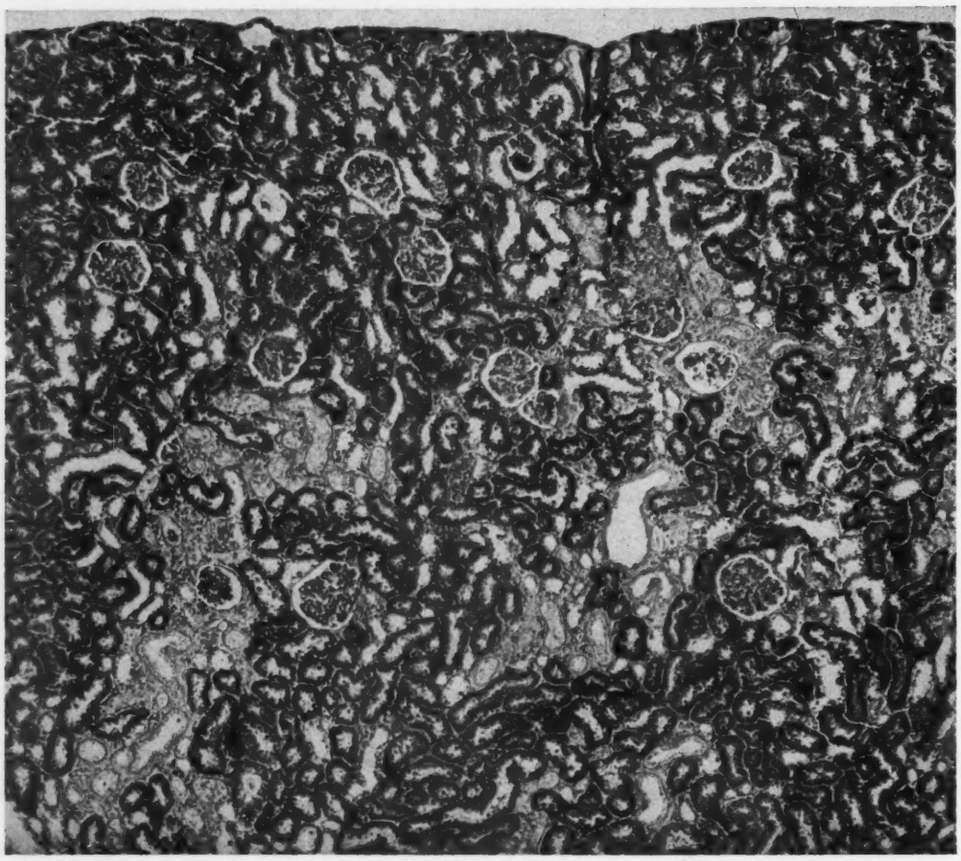


FIG. 23. Cortex of rat kidney stained with iron hematoxylin fifty days after standard dosage of sublimate. Most of the cross sections of proximal convolution are filled with the dark-staining mitochondrial rodlets. Lighter islands of tubular cross section remain in which these intracellular structures are absent.

cellular rodlets that so completely fill the epithelium of the tubules where regeneration is completed. (Fig. 24.) If the sections are stained to show their enzymatic content of lipase (Fig. 25) and alkaline phosphatase (Fig. 26), the immature regenerated tubule cells in these areas are devoid of enzyme.

We can accept these findings, I believe, as a morphologic demonstration of a functional intracellular enzymatic deficiency that results from an observable structural defect, namely, the absence of mitochondrial organs in the immature regenerated renal cells. Thus the functional-structural correlation is pushed one step further back to the elemental level of enzyme and intracellular organella.

This suggestion may seem to some so much an oversimplification as to derive from a somewhat naive view of the dynamic complexities of vital phenomena, but the morphologist by nature and training is, in the charitable sense of the phrase, a simple-minded fellow and it is his business to describe and believe what he sees. If he is not yet entirely clear how "phosphatase" and "lipase" are concerned in the transport of electrolytes across the tubule wall, it nevertheless may be admitted that the ever-shifting structural patterns he sees in the regenerating tubular epithelium as they slowly evolve from amorphous cell complex to the full-blown maturity of their original configuration, replete with mitochondrial, enzymes-containing organelles—all this makes at least a series of pictures to "illustrate" if they do not entirely "explain" the slow and protracted course of renal recovery.

This final correlation at the intracellular level between the structural aspect and the functional expression of tubular activity emphasizes again the essential part played by relative time factors in shaping the pattern of renal recovery. Glomerular structural and functional restitution is, one might say, immediate to the restitution of blood flow; tubular structural and functional recovery require weeks for their completion

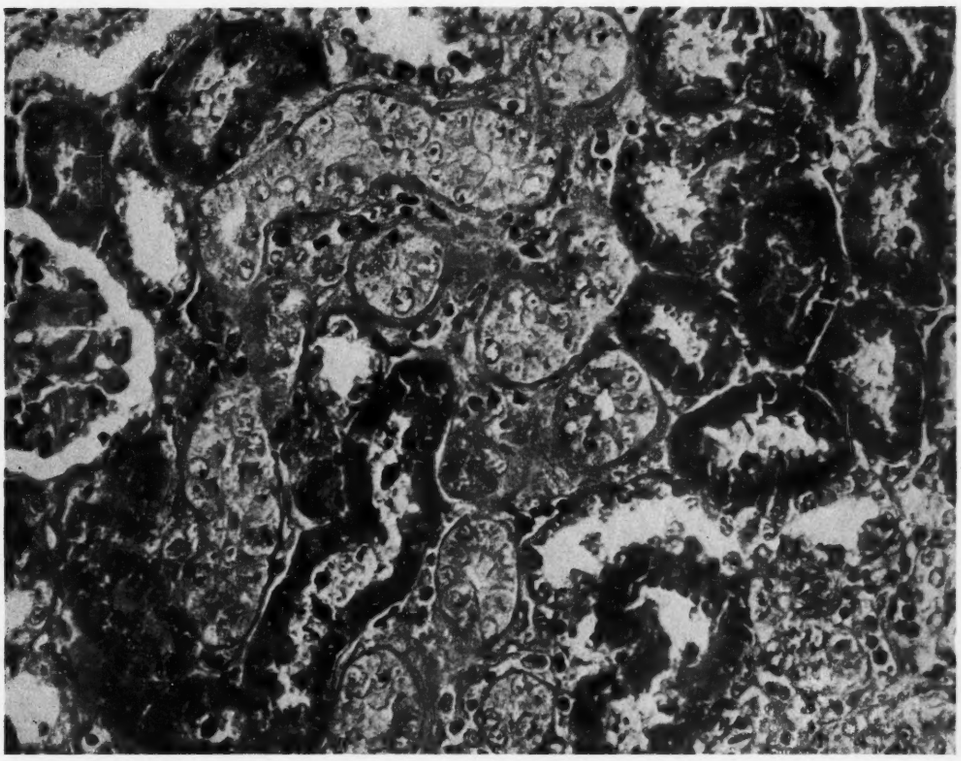


FIG. 24. Higher magnification showing normal proximal convolutions and their mitochondrial rodlets surrounding others lined with an atypical, immature epithelium with no mitochondrial organelles.

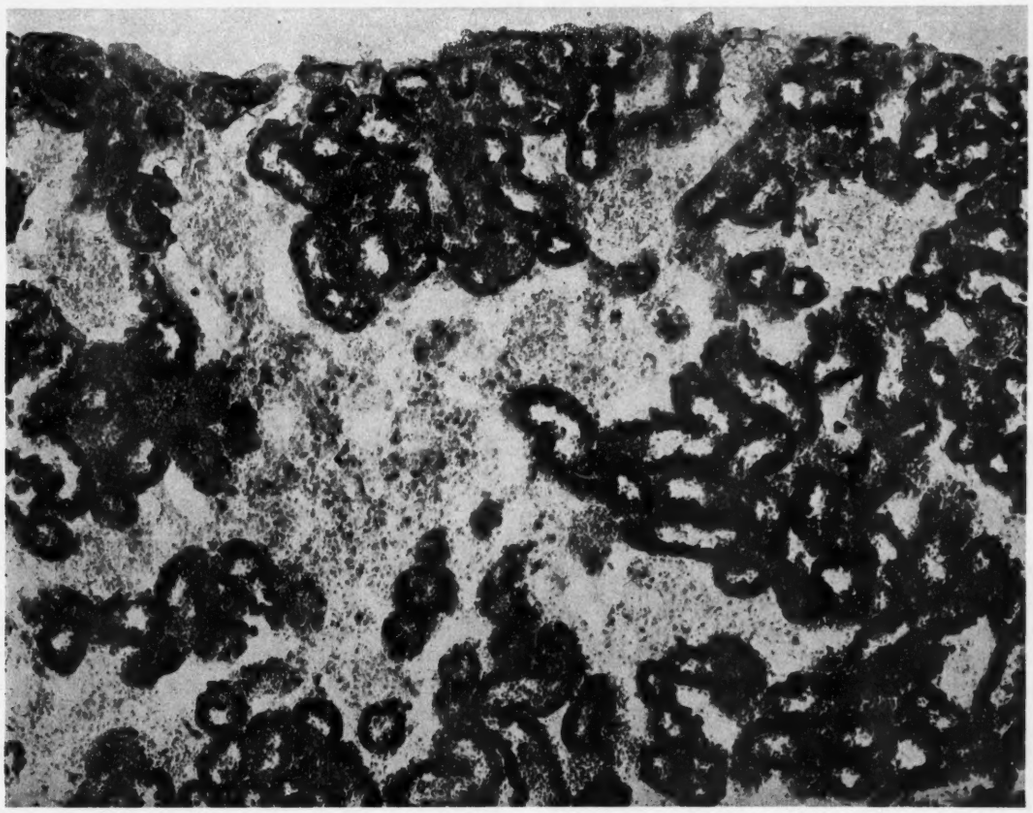


FIG. 25. Same kidney stained for lipase. The enzymatic reaction is sharply positive in proximal convolutions except in the scattered islands of immature epithelium which (cf. Fig. 23) contained no mitochondrial rodlet.

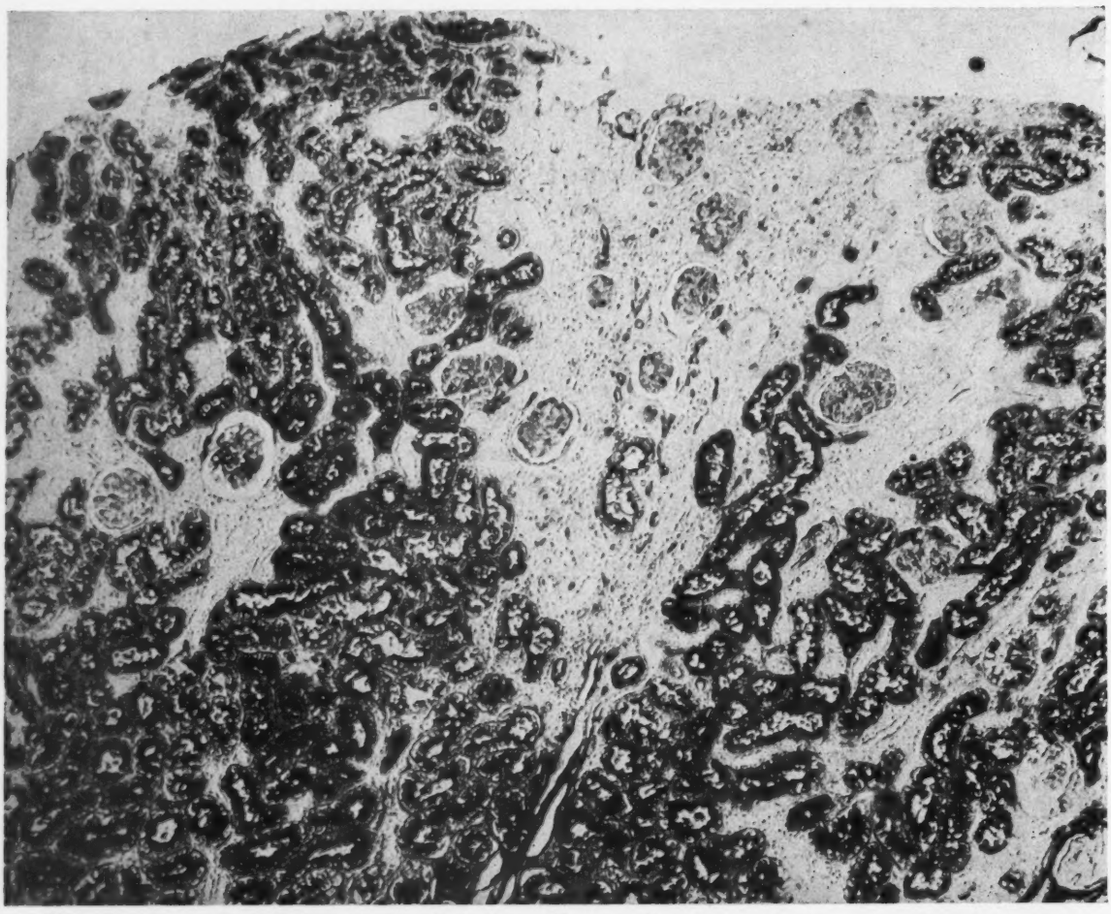


FIG. 26. Same kidney stained for alkaline phosphatase. Similar distribution of enzymatic activity with absence in scattered areas of immature regenerated tubules.

since they depend on the cellular maturation of the new-formed tubular epithelium. It is because of this incongruity that the phenomena of recovery take the form of a diuresis and that this diuresis shifts from its early to late phase as the renal cells develop their essential enzymatic organelles.

It is of some interest to consider in passing how the description I have given of the functional and structural aspects of the diuresis discloses the significance of this peculiarly ambiguous phenomenon. At first glance it is so obviously the antithesis of the oliguric phase and, as the latter is the dire consequence of glomerular and tubular damage, so is it the harbinger of recovery and the expression of the reparative processes. But considered more closely, diuresis, the functional resultant of ill coordinated reparative structural changes in glomerulus and tubule, acts not beneficially towards recovery but blindly and automatically towards depletion of the organism of its essential electrolytes. The chief endeavor of Dr. Bull's treatment is in fact directed towards obviating the ill effects of these "reparative processes" in an attempt to tide the individual over until the slowly progressive maturation of new tubule cells can solve the problem of a concomitantly effective elimination and conservation. The patient in acute renal failure is therefore confronted with two hazards in series; the first, in the oliguric phase, of a death from "uremia," and then again when the diuresis, which has not eliminated the burden of accumulated waste products, adds the ill effects of electrolyte depletion. The majority of the fatalities, in fact, occur during the "recovery period" as a result not so much of the processes of renal damage as of the mechanisms of renal repair. As pathologists we are perhaps not surprised when the "wisdom of the body" seems at times a bit short sighted: however perforce as optimists we must

believe that in the evolutionary long run doubtless Nature knows best or we should not be discussing the matter now.

The consideration of the correlations of structure and function that we have observed are summarized in Table 1. It is obvious that such Procrustean treatment involved a considerable use of expository violence, not only in its disruption of a progressive continuum into neatly disarticulated parts and the stowing of them, each into its proper compartment, but also in the demand that it makes for categorical and oversimplified terseness of statement. Apart from these faults of oversimplification, which are inherent in all such recapitulations, the fact that a tabulation can be made at all is a con-

TABLE 1

CORRELATIONS OF STRUCTURE AND FUNCTION IN ACUTE RENAL FAILURE (ACUTE TUBULAR NECROSIS)

Etiologic Factors	
1. Functional evidence of dual etiology—ischemia and renal poison	1. Two types of tubular lesion—tubulorhexic and nephrotoxic 2. Visual demonstration of focal ischemia in renal poisoning
Functional Disturbances	**Structural Changes**
The Oliguric Phase*	
1. Reduction in RBF and GF	1. Glomerular capillaries empty with tufts collapsed but intact
2. Albuminuria	2. Protein in capsular space
3. Hemoglobinuria	3. Heme pigments in capsular space and tubule lumens, heme casts
4. Loss of proximal tubule function; inability to concentrate urea and creatinine, to conserve electrolyte and to extract PAH	4. Beginning tubular damage—lack of proximal absorption of heme pigments, increasing to tubulorhexic and nephrotoxic necrosis
5. Relative maintenance of glucose Tm	5. Structural integrity of first one-third proximal convolution
6. Persistence of reduced RBF after initial insult	6. Tubular leakage, interstitial edema and reaction and increased intrarenal tension
The Early Diuretic Phase **Occurrence of Diuresis as Result of Reparative Phenomena**	
1. Onset of diuresis as a result of absorption of interstitial edema, increasing blood flow and filtration with continuing depression of tubular absorption of water	1. Distended glomerular capillaries and normal appearing tufts; persisting tubular damage, nephrotoxic and tubulorhexic, with especial involvement of proximal convolution
2. Persisting evidence of abolition of proximal tubule function (lack of ability to concentrate urea in urine, inability to conserve electrolyte or extract PAH.)	2. Extensive atypical regeneration of renal epithelium—absence of mitochondria and consequent reduced enzymatic content of new renal epithelium; excess epithelial proliferation and tubular dilatation
The Late Diuretic Phase	
1. Gradual recovery over weeks or months of tubular functional ability with possible eventual clinical recovery	1. Slowly progressive maturation of regenerated tubular epithelium with ultimate reconstitution of original structures including mitochondrial organelles with their enzymatic content
2. Renal function after clinical recovery adequate but remaining below lower limits of normal[9]	2. Loss of nephrons from irreparable tubulorhexic damage and associated hypertrophy and hyperplasia of others

* See footnote on page 542

siderable achievement, for I believe it is the first time that a major clinical disturbance of renal activity can be described in its total aspect, from onset to recovery, setting against each functional alteration a reasonably apposite and appropriate structural change. This has been accomplished not so much by the concerted effort as through the independent activities of physiologists, clinicians and pathologists working independently and, as it may have seemed at times, at cross purposes; but when the contributions of many minds were brought together, the puzzle solved itself with that apparent automatism which is seemly the miracle of the scientific method.

We pathologists can feel that we have done our proper part, and so we can look back 126 years to the title page that set the terms and stated the solution of modern problems of disturbed renal activity (*see below*). Even its typography should thrill us, for note that it is postulated that the "Symptoms and Cure" are to be illustrated, by a reference to "Morbid Anatomy."

And so they have been; the "symptoms" in these days of modern complexity including such formulistic abstractions as RBF's and Tm_{PAH}'s the "cure" involving procedures that wait on the re-establishment of enzyme-potent rodlets, objects so structurally tangible that anatomists

REPORTS

OF

MEDICAL CASES,

SELECTED

WITH A VIEW OF ILLUSTRATING

THE SYMPTOMS AND CURE OF DISEASES

BY A REFERENCE TO

MORBID ANATOMY.

By RICHARD BRIGHT, M.D. F.R.S. &c.

LECTURER ON THE PRACTICE OF MEDICINE,

AND ONE OF THE PHYSICIANS TO

GUY'S HOSPITAL.

LONDON:

PRINTED BY RICHARD TAYLOR, RED LION COURT, FLEET STREET.

PUBLISHED BY LONGMAN, REES, ORME, BROWN, AND GREEN.

1827.

have collected and biochemists weighed and analysed them.

Apparently, therefore, we have come safely out of that phantasmagorical Looking Glass world through which the functional transcendentalists led us, showing us strange visions of things working by means other than through the operation of their physical constitution.* As pathologists we were perhaps never greatly disturbed by such fantasies, but we did have to listen to considerable hortatory expostulation that we "come out of the dead-house" or that we be "more dynamically functional"! If our contribution to the general effort seemed meagre at time, it was not more functional activity on our part that was needed but, and I use the old word gladly, more morbid anatomy. Today, with the new tools that the physicists and biochemists have prepared for us, we can deliver this ever essential commodity in a new and dynamic aspect.

So we may feel confirmed in our belief that the method we are using is adequate and that the way we are following leads straight. From time immemorial that method has been observation and experiment; that way, a correlative fusion of what, appearing as a duality, is in fact unity, the disease process in its structural and functional aspects. These were the "grand old traditions of the classical curriculum" in the pathology of Gerhard's time; and what is pathology today, if it be not informed with their spirit and attributes?

* Schlayer, K. R. Sic! "Der eine Fundamentalsatz nach dieser Richtung lautet: die Nierenfunktion an sich ist in ihrer Veränderung unabhängig von der anatomischen Art der Erkrankung." *Beitr. zur med. Klin.*, 8: 211, 1912.

REFERENCES

1. Lucké, B. Lower nephron nephrosis (renal lesions of the crush syndrome, of burns, transfusions and other conditions affecting lower segment of nephrons). *Mil. Surgeon*, 99: 371, 1946.
2. Smith, H. The Kidney; Structure and Function in Health and Disease. New York, 1951. Oxford Univ. Press.
3. Bull, G. M., Joekes, A. M. and Lowe, K. G. Renal function studies in acute tubular necrosis. *Clin. Sc.*, 9: 379, 1950.
4. Oliver, J., MacDowell, M. and Tracy, A. The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode. *J. Clin. Investigation*, 30: 1305, 1951.
5. Walker, A. M., Bott, P. A., Oliver, J. and MacDowell, M. The collection and analysis of fluid from single nephrons of the mammalian kidney. *Am. J. Physiol.*, 134: 562, 1941.
6. Dunn, J. S., Gillespie, M. and Niven, J. Renal lesions in two cases of crush syndrome. *Lancet*, 2: 549, 1941.
7. Susuki, T. Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen. Jena, 1912. Fisher.
8. Schlegel, J. U. Demonstration of blood vessels and lymphatics with a fluorescent dye in ultraviolet light. *Anat. Rec.*, 105: 433, 1949.
9. Lowe, K. G. The late prognosis in acute tubular necrosis: an interim follow-up report on 14 patients. *Lancet*, 1: 1086, 1952.
10. Oliver, J. A further study of the regenerated epithelium in chronic uranium nephritis. An anatomical investigation of its function. *J. Exper. Med.*, 23: 301, 1916.
11. Oliver, J., Bloom, F. and MacDowell, M. Structural and functional transformations in the tubular epithelium of the dogs kidney in chronic Bright's disease and their relation to mechanisms of renal compensation and failure. *J. Exper. Med.*, 73: 141, 1941.
12. Schneider, W. C. and Hogeboom, G. H. Cytochemical studies of mammalian tissues: the isolation of cell components by differential centrifugation: a review. *Cancer Research*, 11: 1, 1951.
13. Kabat, E. A. and Furth, J. A histochemical study of the distribution of alkaline phosphatase in various normal and neoplastic tissues. *Am. J. Path.*, 17: 393, 1941.
14. Wachstein, M. Influence of experimental kidney damage on histochemically demonstrable lipase activity in the rat. Comparison with alkaline phosphatase activity. *J. Exper. Med.*, 84: 25, 1946.

Seminars on Neuromuscular Physiology

Inheritance of Diseases Primary in the Muscles*

F. E. Stephens, Ph.D.
Salt Lake City, Utah

Studies of inherited muscular disorders are subject to the same difficulty and inconvenience encountered in any genetic study of human beings. The life span of the geneticist is no longer than that of those whom he studies and the number of generations he can observe is limited; nor can man be studied under conveniently controlled circumstances possible with mice or drosophila. We cannot breed two dystrophic patients to see what would happen; we must wait for two such individuals to make an experiment of their own volition. A review of the reported studies on inherited muscular disorders testifies to the inaccuracies and confusion which are apt to arise.

The inheritance of a defective gene causing a muscular disease may show a wide variation of expression in different individuals. For example, as we shall see, the gene causing myotonia dystrophica may manifest itself through myotonia coupled with muscular dystrophy, cataract and even some mental changes. Yet in some cases its presence is evidenced only by cataract.

This variability in expressivity (the form, or degree, of manifestation) has led some workers to classify certain variations in the expression of a single gene as different disorders with separate patterns of inheritance. Others have grouped together separate disorders as different expressions of the same gene.

Experience has indicated that these errors may be obviated and accurate results best obtained through the study of large family groups. Large pedigrees furnish excellent opportunities to study traits in their different forms of expression. A relatively complete and reliable picture may be obtained when the trait can be observed as it has passed through several generations of the same large kindred.

Experience in family studies has also revealed that great care must be exercised in obtaining data. In casual questioning of a patient about his relatives, information received is very apt to be misleading or at best unfruitful. Secondhand information in genetic studies should be accepted only when actual examinations are impossible and then only with reservations. Also, since reliable genetic ratios are completely dependent on correct diagnosis, it is desirable that the examining physician be one who has observed the trait in question in its various forms of expression.

There are numerous abnormal conditions of the muscles which are usually hereditary. These include such traits as the absence of certain muscles, muscular dystrophies, muscular atrophies and the myotonias. This discussion will be limited primarily to those muscular diseases which have been studied more or less thoroughly at the Laboratory for the Study of Hereditary and Metabolic Disorders at the University of Utah Medical College.

There is need for a more accurate classification of all heritable muscular diseases. This is especially true of the muscular atrophies and the different forms of ataxia. Peroneal muscular atrophy, for example, has been reported as following a dominant, an autosomal recessive and a sex-linked recessive pattern of inheritance. Studies are now in process at our Laboratory

* Work at the Laboratory for the Study of Hereditary and Metabolic Disorders, College of Medicine, University of Utah, (Director, Dr. M. M. Wintrobe) has been supported in part by a grant from the United States Public Health Service and has been done in cooperation with Dr. Frank H. Tyler, Assistant Professor of Medicine and Clinician for the Project.

which, it is hoped, will help clarify our understanding of the mode of inheritance of these muscular disorders.

MUSCULAR DYSTROPHIES

Progressive muscular dystrophy is perhaps the most important and best known group of the inherited muscular disorders.

Aran[1] and Meryon[2] were the first to distinguish the muscular dystrophies, in which the primary cause of muscular wasting is located in the muscles, from muscular atrophy, in which the primary defect is in the nervous system. Earlier workers, however, had described cases of muscular dystrophy. While isolated sporadic cases may arise, there is a definite tendency for this defect to occur in more than one member of a kindred and to follow a certain genetic pattern. The variability of its expression and the similarity of the different genetic types have led to difficult problems of classification. Many workers have considered all cases as merely different expressions of the same disease. In 1943 Julia Bell[3] made an extensive review of all the work which had been done prior to that time. She concluded that all types of muscular dystrophy are caused by the same gene and that differentiation is due to different modifying factors. These conclusions were based upon a review of the literature and not upon original study. Such conclusions are subject to whatever inaccuracies and confusion may be inherent in the original reported studies.

Extensive studies of large family groups at our Laboratory have led to the conclusion that most cases of progressive muscular dystrophy can be classified into two general groups, each of which is inherited as a separate genetic entity, following a different pattern of inheritance. These are facioscapulohumeral progressive muscular dystrophy and childhood progressive muscular dystrophy. The former group encompasses Erb's[4] "juvenile dystrophy" and the type of "Landouzy and Déjerine";[5] the latter comprises most of the patients included in the literature under the headings "pseudohypertrophic," "simple atrophic," "Duchenne"[6] and "Leyden and Moebius" types.

Facioscapulohumeral Progressive Muscular Dystrophy. This disease is characterized by a wasting away of certain muscles. Expression of the trait ranges from a degree which completely incapacitates individuals to that in persons who, although they may be well advanced in years, are hardly aware of the affliction. Symptoms which the patient or his family can observe usually appear between seven and twenty years of age. The most frequent age of onset is between thirteen and fifteen years. Weakness normally occurs first in the shoulders, face or arms (hence the term facioscapulohumeral muscular dystrophy).

The first noticeable symptom is usually the inability to raise the arms above the head. Winged scapulae appear and dystrophy is manifested in other muscles. In cases in which the face is affected, it becomes impossible to pucker the lips, as in whistling, and there is a peculiar expression to the face when the patient attempts to smile. A flattened chest and a peculiar gait are also characteristic of the disorder. The dystrophy progresses with the age of the individual, sometimes continuing until late in life and in other cases halting at an early age. It occurs as often in males as in females. Mental traits appear to be unaffected.

Inheritance: Facioscapulohumeral muscular dystrophy was first described in 1885 by Landouzy and Déjerine.[5] They reported nine cases in four generations of one kindred, with the second generation showing no affected individuals. Eulenberg and Cohn,[7] Weitz,[8] Niwa,[9] Sidler[10] and others suggested a pattern of dominant inheritance, although the numbers affected in any one family were relatively small.

Eight kindreds showing this disorder have been investigated at our Laboratory.[11] All showed the same general clinical manifestations of the disease and the same type of inheritance. Whether or not the same gene is involved in all of these kindreds is not completely certain. Figures 1 and 2 show pedigree charts of one of these kindreds. A total of 1,249 individuals were considered in this kindred, 159 of whom had muscular dystrophy.

In analyzing these data only those families for which accurate information for nearly all the members was available were used. Because identification of the disorder in children under twelve is difficult, families with many children below this age were eliminated. Examinations by physicians were made whenever possible; where they could not be made, a careful family history was obtained from available members of the family familiar with the cases.

Our studies revealed that the trait occurred only in the children of an affected parent. This can be seen in Figures 1 and 2 in kindred

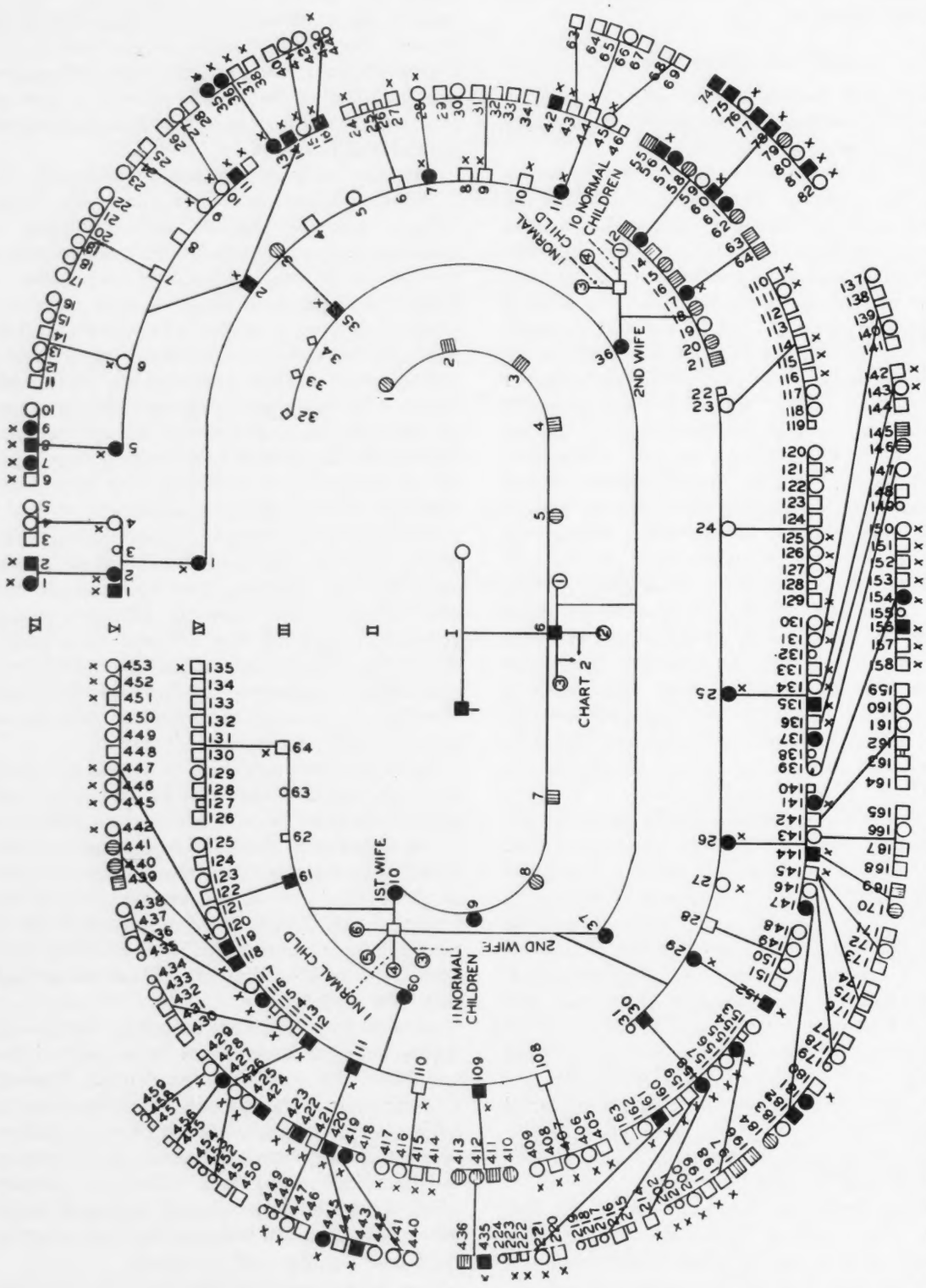


FIG. 1. Pedigree of facioscapulohumeral muscular dystrophy. The descendants of II-6 and his second and third wives are diagrammed separately in Figure 2. (From TYLER and STEPHENS, *Ann. Int. Med.*, 1950.)

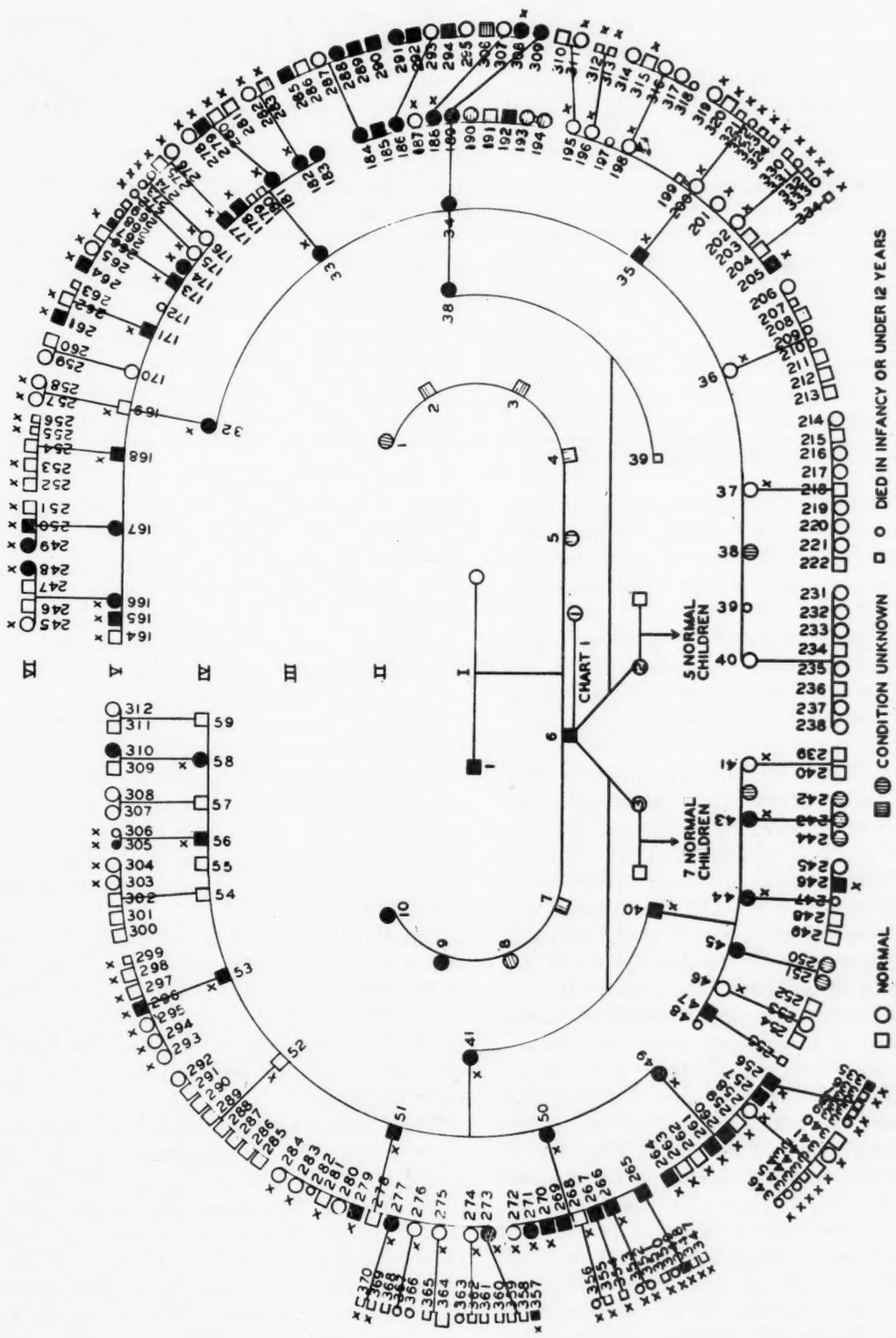


FIG. 2. Pedigree of facioscapulohumeral muscular dystrophy. The descendants of II-6 and his first wife are diagrammed separately in Figure 1. (From TYLER and STEPHENS, *Ann. Int. Med.*, 1950.)

2. There were fifty-four families in this kindred in which one parent showed the trait, and the data were sufficient to permit the family to be used. As shown in Table 1 these families produced 273 children, of whom 130 were affected and 143 were normal. This is a simple 1:1 ratio of normal to affected individuals, which is what would be expected in a typical "back-cross" (Dd × dd). The deviation divided by the standard error (D/SE) is only .79 which is not significant.

TABLE 1

A COMPARISON OF THE NUMBER OF DYSTROPHICS WITH THE NUMBER OF NORMAL OFFSPRING IN FAMILIES IN WHICH ONE PARENT IS DYSTROPHIC*

Phenotypes	Observed	Calculated	Deviation	Standard Error	D/SE
Normal (dd)	143	136 5	6.5	8.26	.79
Dystrophic (Dd)	130	136.5	6.5		
Total	273	273.0	...	....	...

* From Tyler and Stephens, *Ann. Int. Med.*, 1950.

It will be seen from the pedigree that there were several polygamous marriages. II-6, an affected male, married three non-affected wives, two of whom had children by former marriages. Dystrophy occurred in some of the offspring of all three marriages with the dystrophic father, but no cases occurred in the children or in descendants of the former marriages of the two wives. The husband of II-10 and III-37, both of whom were affected, had four other wives, none of whom had dystrophy. The disease occurred only in the descendants of the affected wives. This is also true in the descendants of the other wives of the polygamous husband of III-36.

These facts indicate a simple autosomal dominant pattern of inheritance with wide variability in expression and complete penetrance. (If the disease is expressed in any form, the "penetrance" is considered complete.) This implies that each individual showing facioscapulohumeral progressive muscular dystrophy stands a fifty-fifty chance of transmitting the disorder to his children. Persons who do not have the disorder cannot transmit it. We have been unable to find any instance in which two dystrophics have married. It is, therefore, impossible to determine whether the disorder would manifest itself any differently in a homozygous individual. Dominance may be incomplete, or the homozygote might even be lethal.

As noted previously there is a wide variation in the expression of the disorder. This does not mean, however, that these variations result from the effect of several independent genes. Mildly affected parents may have severely affected children; and conversely, severely affected parents may have only slightly affected children. This indicates the action of a single gene, expressing itself in a variable manner in different individuals. The variation apparently results from other genetic differences in the individuals or from environmental factors.

Childhood Progressive Muscular Dystrophy. The term pseudohypertropic progressive muscular dystrophy has often been used for this disorder. Childhood progressive muscular dystrophy is a preferable term (Tyler and Wintrobe[12]), since pseudohypertrophy[13] may or may not be present in this disease and it may be present in other types of dystrophy.

Childhood progressive muscular dystrophy differs from the facioscapulohumeral type both in its mode of inheritance and in its pattern of expression. Inconsistencies in the literature have probably arisen largely because this form of dystrophy has been confused with other muscular disorders.

The disease is usually detected[14] at about three years of age. The first symptoms are generally a waddling gait, frequent falling and difficulty in running. As the disease progresses, a characteristic pattern of muscular atrophy and weakness develops. Pseudohypertrophy occurs in many but not in all cases. It is often apparent in the calf muscles which have the appearance of strength but are actually very weak. These muscles show infiltration of fat and fibrous tissue which usually persists throughout life.

The disease progresses until, by the age of nine to twelve, the majority of children are wheel chair cases. Death usually comes from intercurrent respiratory infections in adolescence or early adult life.

Inheritance: As early as 1879 Gowers[15] pointed out that the type of pseudohypertrophic muscular dystrophy which occurs early in life is probably transmitted by normal mothers to their sons, while the type which occurs later in life may sometimes be transmitted by their fathers as well. It is possible that he was confusing the facioscapulohumeral and the childhood types. Later the works of Voshell,[16] Kostakow,[17] Arbuse and Sloane,[18] and others[19] suggested sex-linked recessive inheritance.

The disorder seldom occurs in more than ten members of a kindred and in many instances occurs in only one or two. For this reason it is a decided advantage to investigate the condition in several different kindreds. At the University of Utah thirty-three kindreds involving 1,977 normal and sixty-five affected individuals have been studied.[20] The trait occurred only in males and the same general pattern of expression was found in all affected individuals.

In analyzing the data the kindreds were classified into three groups. In Group I the defective gene could be traced down through a line of female carriers from the first known female in the kindred to the affected individuals. This suggests a pattern of recessive sex-linked inheritance in which the defective gene is located on the X chromosome. In none of the kindreds in this group or in Groups II and III could the possibility of this pattern of inheritance be eliminated. It should be noted, however, that since the affected males never reproduced, it is conceivable that the disorder may result not from a sex-linked recessive gene but from an autosomal gene expressing itself in the heterozygous condition in males but not in heterozygous females. This reservation must qualify the conclusion that a recessive sex-linked gene is involved.

The disease in the kindreds of Group II could be due to a recessive sex-linked gene, but there were not enough males in a direct line from the first known female to the affected descendants to establish definitely whether or not this pattern of inheritance was followed.

The kindreds in Group III presented a more difficult problem. Here there were sufficient males in direct line from the first known female to trace the defective gene down to the affected individual. However, there were so many unaffected males in the line that it is unlikely that a gene could have been transmitted through such a group without showing up in some of them.

The answer to the problem probably lies in the fact that childhood progressive muscular dystrophy continues to exist in society today in spite of the death of the victims before they reproduce. The disease is so severe that its victims seldom, if ever, reproduce. This means that by a process of natural selection the disorder should be eliminated from the population. But it has not disappeared. A check on cases of childhood dystrophy born in Utah between the years 1930–1940 shows no apparent decrease in the frequency of this disease. A new supply of defective genes must be constantly occurring. The affected individuals in Group III, therefore, probably represent new mutations of the gene.

If this is true, the gene for childhood progressive muscular dystrophy must mutate at a comparatively high rate. During the period 1930–1940 there were six dystrophic individuals born who were classified in Group III. State Vital Statistics show that approximately 126,000 children were born in Utah during this period. If one-half of these were males, the total group would represent 189,000 X chromosomes, since each female has two X chromosomes and each male has only one. Therefore, one-third of the total, or 63,000 X chromosomes, occurred in the males. Six mutations appear to have occurred in this one-third, so 6/63,000 gives the approximate minimum mutation rate, or approximately 1×10^{-5}. Any cases which might have been missed or may have occurred in Group II would only slightly increase this rate. This is one of the highest mutation rates reported in human beings.

MYOTONIA

The inherited myotonias make up another group of muscular disorders. Myotonia is a peculiar functional disturbance characterized by a delayed relaxation of the muscles after contraction. Where it follows voluntary contraction, it is called active myotonia; where it follows mechanical stimulation, it is called mechanical myotonia. Three hereditary forms are known, myotonia congenita or Thomsen's disease, paramyotonia and myotonia dystrophica. They are closely related clinically and are not always described as separate diseases.

Julia Bell,[21] Maas and Paterson,[22] and others have taken the view that they are all expressions of the same genetic disorder. Data assembled at our Laboratory do not support this view. There is good evidence that they are separate disorders, each due to a separate gene.

Myotonia Congenita. Myotonia congenita, or Thomsen's disease, is not common. It has been reported, however, in Japan, many European countries and the United States. Ordinarily it becomes evident in early childhood or it may be congenital. Muscular hypertrophy is common in this condition. Myotonia is usually found throughout the striated muscles of the body, although it is more pronounced in some muscles than in others. It is sometimes localized in certain muscle groups. Indeed, Thomasen[28] has stated that localization in the facial and ocular muscles is almost a specific feature of the disorder. Localization in the hands and legs is also common. The patient often experiences difficulty in such activities as climbing stairs or straightening fingers after clenching the fist. A stiffness characteristically occurs, which tends to disappear upon repeated contractions of the muscles concerned. Cold temperatures, emotional distress and fatigue may influence expression of the trait.

Inheritance: In 1876 a Danish doctor, Asmus Julius Thomas Thomsen,[23] described the disorder in himself and in other members of his family. In 1881 Strümpell[24] gave it the name myotonia congenita and Westphal[25] designated it as Thomsen's disease in 1883. Erb[26] wrote an exhaustive clinical description of the disease in a classic monograph in 1886. The study of Thomsen's family was later continued by his grandnephew, Nissen,[27] in 1923, and more recently (1948) by Eivind Thomasen.[28] The disease has been traced back in this family to the year 1742. This is probably the largest and most complete study made of the disorder. It includes seven generations with sixty-four cases of the defect.

It is quite evident that myotonia congenita in this family is inherited as a simple dominant trait. It occurs approximately as often in males as in females (34 males:30 females). In this family no two affected individuals ever married. Therefore, it is impossible to say whether or not dominance is complete. However, te Kamp[29] reports a family in which both parents were affected with the disease. Of their nine children, five were stillborn. This suggests that the homozygote may be less apt to survive than the heterozygote.

After the studies of Thomsen[23] and Erb[26] other workers described cases of myotonia which seemed to differ in many respects from Thomsen's disease. In the course of time two additional disorders have been distinguished, namely, paramyotonia and myotonia dystrophica.

Paramyotonia. Eulenburg[30] in 1886 described a family showing a form of myotonia brought on by cold. He called the condition paramyotonia. By 1916 when this family was again studied, the disorder could be traced through eight generations. A similar condition was reported in Holland by Delprat,[31] van der Stock[32] and Sanders.[33]

In 1894 Ezra Rich[34] described a kindred similar to that studied by Eulenburg. Seventeen members of this kindred showed the trait. This same kindred has been investigated recently at our Laboratory, and it has been possible to trace the disease in a direct line through seven generations. Sixty-two affected individuals are now known to have had the trait.

Paramyotonia in this kindred is expressed as an immobility of the muscles brought on by cold. The hands and face or other exposed parts are most often affected. The application of an eye cup filled with cold water to the eye for a short time, or of an icepack to one side of the face, causes the muscles of the eye or face to become immobile while adjoining muscles continue to function normally. Ice or snow taken into the mouth produces the same result on the tongue. Immobility may last from a few minutes to a few hours. There is no pain. The trait becomes evident in the first year of life. One patient reported an experience occurring while she was attending a university summer school class. After perspiring freely on a hot day while hurrying to class, she sat in a draft by an open window. At the end of the class period she was unable to rise from her seat to leave the room. Not until two students had helped her to her feet and walked her about for a while was she able to walk home alone.

There is a close relationship between myotonia congenita and paramyotonia. Cold temperatures increase the myotonia in myotonia congenita. Slight myotonia, without the application of cold, has been found occasionally in paramyotonia.

Inheritance: It is interesting to note that Rich reported his family six years before the discovery

of Gregor Mendel's paper. Referring to the heredity of the trait he states, "I believe the foregoing history of this curious form of motor paralysis establishes its heredity beyond doubt. The peculiarity never skips one generation and appears in the next. The family is aware of the fact and knows when a child does not inherit the affliction it is ended as far as his offspring are concerned."

Rich here described a dominant trait but, of course, attempted no explanation for its behavior. The trait occurs in the children only when it occurs in one of the parents. Males and females are affected with the same approximate frequency, and one-half of the offspring of affected parents show the trait. The actual ratio in affected families of this kindred is sixty-one affected to sixty normal individuals. This presents a clear picture of the behavior of a simple autosomal dominant trait. Since no two affected individuals married, it is not possible to tell if dominance is complete.

Myotonia Dystrophica. This disease is both the most common and the most severe of the myotonias. Hoffmann[35] first described it in 1896, but thought it was Thomsen's disease complicated by neuritis. Steinert (1909)[36] was possibly the first to show that it is a specific disease separate from myotonia congenita. Curschmann's work, from 1912 on,[37–39] confirmed the findings of Steinert. He gave the disease the name dystrophia myotonica and showed that it differed clinically and genetically from myotonia congenita.

Clinically, the disease is a syndrome having one or more of a group of characteristics. Myotonia is generally present and is usually localized in certain muscle groups, particularly in the finger flexors. It may occur in the tongue and muscles of mastication, or, more rarely, in the leg or other muscles.

Muscular dystrophy is also a characteristic of the syndrome. Dystrophy is found in muscles of the face and neck, the sternomastoid muscles and in the muscles of mastication. It may spread to the muscles of the forearms and the legs, giving the patient a peculiar gait. The voice is often affected, producing a low nasal tone. The head droops forward and the mouth may hang partially open due to weak muscles of mastication. There is often a "hatchet face" appearance. Gonadal dystrophy and sterility are very common in severe cases. Baldness is a frequent characteristic, but may not always be present even in severe cases. With rare exceptions lenticular opacities, or cataract, occur. Sometimes this is the only indication that the individual is affected. Mental changes may appear which suggest some intellectual deterioration. Indolence, carelessness, lack of initiative, etc., are characteristic in many individuals.

The age of manifestation of the disease has been reported to vary from two to over fifty years. It begins most frequently between fifteen and twenty years of age. The disease is progressive in nature. The later the age of onset, however, the less severe is the expression of the trait. Most patients die before the age of fifty.

Inheritance: Wide variation in expression and in age of onset makes myotonia dystrophica very difficult to trace in family pedigrees. From the data available, however, there is good evidence that in most cases the disease is inherited as a simple dominant trait. Fleischer,[40,41] Frey,[42] Henke and Seeger,[43–45] and Thomasen[28] all came to this conclusion.

Thomasen studied the disease in twenty-one families. He traced it through three generations in three families, through two generations in eleven families and through one generation in seven families. By supplementing the pedigrees with information concerning dead family members, he followed it through four generations in ten families. In every case in which he was able to examine both parents of a patient, one always showed some manifestation of the disease, although in some cases cataract was the sole indication of the trait.

At our Laboratory the study of pedigrees showing myotonia dystrophica has demonstrated simple dominant inheritance. The disease has occurred only in children of an affected parent and has appeared as often in males as in females.

Many workers have reported that anticipation with potentiation (increased severity) is present in myotonia dystrophica. They report that the disease appears earlier and is more severe in each succeeding generation. Penrose[46] concluded from Julia Bell's[21] data that such anticipation was present. He proposed a possible genetic explanation. Studies of drosophila and other organisms have shown that various normal "alleles" may be present in individuals which produce no effect unless in heterozygous combination with a gene which causes defects. According to this theory the disease was deter-

mined by a dominant gene "M" and its severity of expression by the alleles m_1 or m_2 which occur in the general population. A combination of M and m_1 produces severe manifestations with onset at an early age, while the genotypic combination Mm_2 produces a milder form of the disease with a later onset. If an affected parent happened to marry a normal individual homozygous for m_1, in all the affected children the age of onset would be early and, therefore, the expression of the disease would be more severe. This theory would also explain the fact that Julia Bell's data showed a greater similarity between siblings than between parents and children.

There is some doubt, however, whether anticipation with potentiation actually exists in this disease. Several factors could lead to incorrect conclusions on this point. Even where physical examinations are made, slight cases may be ignored since the manifestations are often difficult to discover—especially when slit lamps are not available. Information from relatives is misleading since very probably slight cases would be missed and information concerning age of onset would also be very inaccurate. Indeed, experience has shown that information from patients themselves as to age of onset is unreliable. These factors could result in selection in the data which may give results erroneously suggesting anticipation. This impression might also arise from the fact that most severe cases can be traced back to less severely affected parents. This is true because severely affected patients are sterile and would have no children.

These conditions make it hazardous to conclude that anticipation with potentiation exists until careful studies have been made of an abundance of data concerning several generations in the same kindred.

FAMILY PERIODIC PARALYSIS

Many workers have reported the inheritance of what is referred to as family periodic paralysis.[47] It is evident that all the cases described in the literature are not due to the same mutation. They appear to follow different patterns of inheritance. There is a wide variety in the clinical characteristics described. There has been variability in severity and duration of paralysis, association with other defects, age of onset and other clinical manifestations. The reported patterns of inheritance also differ. Complete dominance,[48,49] dominance with skipped generations,[50,51] simple autosomal recessive[47] and recessive sex-linked patterns[52] have been found. In some cases there has been incomplete penetrance in females;[47] in others, penetrance was complete in both sexes.[49]

A large kindred showing family periodic paralysis in thirty-three individuals in seven generations was studied at our Laboratory.[53] In this kindred the trait is characterized by the onset of weakness or paralysis in the large voluntary muscles. Males are affected as often as females. The attacks may occur at any time but come most frequently in the early morning. Often the attacks occur during a period of inactivity following a period of physical exertion. Emotional stress may induce an attack. When attacks are felt to be coming on, activity tends to ward them off. Paralysis may begin in the shoulders, or back, or in the extremities, and gradually spreads to all parts of the body until the individual is unable to move a muscle. During a severe attack the individual is unable to move any of the voluntary muscles. Often, enlargement of the muscles, particularly those of the calf, is evident. The duration of the paralysis varies from a few minutes to two or three days, the average period being about one hour. The episodes vary in frequency. They may occur daily or several may occur during the same day, or several days may intervene between attacks. Serum potassium values have been consistently normal during and between attacks. The use of potassium chloride was not effective in influencing the course of the disorder.

The age of onset is very early in infancy. Mothers familiar with the disease can identify it by the peculiar cry of an affected baby at two or three months of age. Since it is so easily identified and occurs at such an early age, its genetic study is very much simplified.

Inheritance. In the kindred studied at the University of Utah, the trait occurred as often in males as in females and never was expressed unless one of the parents was affected. There was no case in which two persons with the disease married, so each affected individual is heterozygous for the trait. The crosses, therefore, would all be "back-crosses" and the children of an affected parent should be in the ratio of one affected to one normal child. The actual results are shown in Table II.

An examination of Table II shows that the trait is inherited in this kindred as a simple

mendelian dominant. Since no two persons suffering from the disorder married, homozygous patients could not be produced. It was not possible, therefore, to determine whether or not dominance was complete.

SUMMARY

1. Hereditary muscular diseases can best be studied in large family groups in which the variety of expressions of the same gene can be identified. Extending examinations by physicians to greater numbers of individuals in kindreds being studied will also add much to our understanding of these diseases and our knowledge of the pattern of their inheritance.

2. Progressive muscular dystrophy is perhaps the most important and best known group of muscular disorders.

3. Most cases of progressive muscular dystrophy can be classified into two general groups, the facioscapulohumeral type and the childhood type. Each of these is inherited as a separate genetic entity following a different pattern of inheritance.

4. Facioscapulohumeral progressive muscular dystrophy varies in its form of expression. Its age of onset is usually between seven and twenty years. It is inherited as an autosomal dominant.

5. Childhood progressive muscular dystrophy differs from facioscapulohumeral muscular dystrophy both in its mode of inheritance and in its pattern of expression. The age of onset is usually about three years. There is good evidence that it is inherited as a sex-linked recessive trait.

6. The gene producing childhood muscular dystrophy has a high mutation rate. Its minimum mutation rate is roughly estimated at one in 10,000 (approximately 1×10^{-5}).

7. Three types of myotonia are discussed, myotonia congenita (Thomsen's Disease), paramyotonia and myotonia dystrophica.

8. Myotonia congenita is not a common disease. It is congenital or can be identified at a very early age. It is inherited as an autosomal dominant.

9. Paramyotonia is a rare disease. It is expressed as an immobility of the muscles brought on by cold. It can be detected when a child is but a few months old and is inherited as an autosomal dominant.

10. Myotonia dystrophica is the most common as well as the most severe form of the myotonias. It is inherited as an autosomal dominant with a wide variability of expression.

11. It is evident that all cases of family periodic paralysis described in the literature are not due to the same mutation. In the kindred studied at the University of Utah the defect was inherited as an autosomal dominant.

12. Since the traits described as being due to autosomal dominant genes have not occurred in the homozygous condition it cannot be determined whether or not dominance is complete or what the expression of the homozygote is.

TABLE II

STATISTICAL COMPARISON OF DATA ON KINDRED WITH PERIODIC PARALYSIS WITH THE THEORETIC BEHAVIOR OF A DOMINANT TRAIT*

Phenotypes	Observed	Calculated	Deviation	Standard Error	D/SE
Normal (pp)	36	34	2	4.12	.485
Affected (Pp)	32	34	2		
Total	68	68	.	....	....

* From Tyler, Stephens, Gunn and Perkoff, *J. Clin. Investigation*, 1951.

REFERENCES

1. ARAN, F. A. Réchèrches sur une maladie non encore décrite du système musculaire. (Atrophie musculaire progressive.) *Arch. gén. de méd.*, 24: 5, 172, 1850.
2. MERYON, E. On granular and fatty degeneration of the voluntary muscles. *Med. Chir. Trans.*, 35: 73, 1852.
3. BELL, J. On pseudohypertrophic and allied types of progressive muscular dystrophy. In: Treasury of Human Inheritance, vol. 4, part 4. New York, 1943. Cambridge University Press.
4. ERB, W. Ueber die juvenile Form der progressiven

Muskelatrophie. *Deutsches Arch. f. klin. Med., Leipz.*, 34: 467, 1884.

5. Landouzy, L. and Déjerine, J. De la myopathie atrophique progressive. *Rev. med. franç.*, 5: 81, 1885; 5: 253, 1885; 6: 977, 1886.
6. Duchenne, G. B. Réchèrches sur la paralysie musculaire pseudohypertrophique, ou paralysie myosclerosique. *Arch. gén. de méd.*, 11: 5, 179, 305, 421, 552, 1868.
7. Eulenburg, A. and Cohn, T. Inheritance of facioscapulohumeral dystrophy. *Neurol. Centralbl.*, 30: 963, 1911.
8. Weitz, W. Ueber die Vererbung bei der Muskeldystrophie. *Deutsche Ztschr. f. Nervenh., Leipz.*, 72: 143, 1921.
9. Niwa, C. Über den Vererbungsmodus von Dystrophia musculorum progressiva. *Proc. Imp. Acad.*, 5: 287, 1929.
10. Minkowski, M. and Sidler, A. Klinische und genealogische Untersuchungen zur Kenntnis der progressiven Muskeldystrophie. *Arch. d. Julius Klaus- Stift. f. d: Vererbgsforsch.*, 239, 1928.
11. Tyler, F. H. and Stephens, F. E. Studies in disorders of muscle. II. Clinical manifestations and inheritance of facioscapulohumeral dystrophy in a large family. *Ann. Int. Med.*, 32: 4, 640, 1950.
12. Tyler, F. H. and Wintrobe, M. M. Studies in disorders of muscle. I. The problem of progressive muscular dystrophy. *Ann. Int. Med.*, 32: 72, 1950.
13. Tyler, F. H. Studies in disorders of muscle. III. "Pseudohypertrophy" of muscle in progressive muscular dystrophy and other neuromuscular disorders. *Arch. Neurol. & Psychiat.*, 63: 425, 1950.
14. Tyler, F. H. and Stephens, F. E. Studies in disorders of muscle. IV. The clinical manifestations and inheritance of childhood progressive muscular dystrophy. *Ann. Int. Med.*, 35: 169, 1951.
15. Gowers, W. R. Pseudohypertrophic Muscular Paralysis. London, 1879. J. and A. Churchill.
16. Voshell, A. F. Progressive pseudohypertrophic muscular dystrophy. *South. M. J.*, 26: 156, 1933.
17. Kostakow, S. Die progressive Muskeldystrophie, ihre Vererbung and Glykokollbehandlung. *Deutsches Arch. f. klin. Med.*, 176: 467, 1934.
18. Arbuse, D. I. and Sloane, D. Muscular dystrophy: report of a family. *New York State J. Med.*, 37: 1111, 1937.
19. Polacheck, W. S. Heredity of pseudohypertrophic muscular dystrophy. *Am. J. Dis. Child.*, 61: 1251, 1941.
20. Stephens, F. E. and Tyler, F. H. Studies in disorders of muscle. V. The inheritance of childhood progressive muscular dystrophy in 33 kindreds. *Am. J. Human Genet.*, 3: 111, 1951.
21. Bell, J. Dystrophia myotonica and allied diseases. In: Treasury of Human Inheritance, vol. 4, part 5. New York, 1947. Cambridge University Press.
22. Maas, O. and Paterson, A. S. The identity of myotonia congenita (Thomsen's disease), dystrophia myotonica (myotonia atrophica) and paramyotonia. *Brain*, 62: 198, 1939.
23. Thomsen, J. Tonische Krämpfe in willkürlich beweglichen Muskeln in Folge von ererbter psychischer Disposition. *Arch. f. Psychiat., Berl.*, 6: 702, 1876.
24. Strümpell, A. Tonische Krämpfe in willkürlich bewegten Muskeln. (Myotonia congenita) *Berl. klin. Wchnschr.*, 18: 119, 1881.
25. Westphal, C. Demonstration zweier Falle von Thomsen'scher Krankheit. *Berl. klin. Wchnschr.*, 20: 153, 1883.
26. Erb, W. Die Thomsen'sche Krankheit. (Myotonia congenita.) Leipzig, 1886.
27. Nissen, K. Beiträge zur Kenntnis der Thomsen'scher Krankheit (Myotonia Congenita) mit besonderer Berücksichtigung des hereditären Momentes und seinen Beziehungen zu den Mendelschen Vererbungsregeln. *Ztschr. f. klin. Med.*, 97: 58, 1923.
28. Thomasen, E. Myotonia: Thomsen's Disease (Myotonia Congenita), Paramyotonia, and Dystrophia Myotonica, vol. 17. Aarhus, 1948. Universitetsforlaget i Aarthus.
29. te Kamp. Ein Beitrag zur Kenntnis der Myotonia congenita, sog. Thomsen'schen Krankheit. *Deutsche med. Wchnschr.*, 33: 1005, 1907.
30. Eulenburg, A. Ueber eine familiäre, durch 6 Generationen verfolgbare Form congenitaler Paramyotonie. *Neurol. Centralbl.*, 5: 265, 1886.
31. Delprat, C. C. Thomsen'sche Krankheit in einer paramyotonischen Familie. *Deutsche med. Wchnschr.*, 18: 158, 1892.
32. van der Stock, J. A. De ziekte van Thomsen beschouwd uit bet oogpunt van geschiktheid of ongeschiktheid voor den militairen dienst en van de gerechtelijke geneeskunde. *Gravenhage* 1893. Cit.: J. Sanders: *Genetica.* 17: 253, 1935.
33. Sanders, J. Eine Familie mit Myotonia congenita (Thomsen'sche Krankheit). *Genetica*, 17: 253, 1935.
34. Rich, E. C. A unique form of motor paralysis due to cold. *M. News*, 65: 210, 1894.
35. Hoffmann, J. Ein Fall von Thomsen'scher Krankheit, compliziert durch Neuritis multiplex. *Deutsche Ztschr. f. Nervenh., Leipz.*, 9: 272, 1896.
36. Steinert, H. Über das klinische und anatomische Bild des Muskelschwunds der Myotoniker. *Deutsche Ztschr. f. Nervenh., Leipz.*, 37: 58, 1909.
37. Curschmann, H. Über familiäre atrophische Myotonie. *Deutsche Ztschr. f. Nervenh., Leipz.*, 45: 161, 1912.
38. Curschmann, H. Beobachtungen und Untersuchungen bei atrophischer Myotonie. *Deutsche Ztschr. f. Nervenh., Leipz.*, 53: 114, 1915.
39. Curschmann, H. Dystrophia myotonica sine Dystrophie. *Deutsche Ztschr. f. Nervenh., Leipz.*, 74: 157, 1922.
40. Fleischer, B. Ueber myotonische Dystrophie. *Münschen. med. Wchnschr.*, 64: 1630, 1917.
41. Fleischer, B. Über myotonische Dystrophie mit Katarakt. *Arch. Ophth.*, 96: 91, 1918.
42. Frey, H. C. Beitrag zur myotonischen Dystrophie. *Arch. f. Rassen-u. Gesellsch.-Biol.*, 17: 1, 1925.
43. Henke, K. and Seeger, S. Progressive Vererbung und Degeneration bei der myotonischen Dystrophie. *Biol. Zentralbl.*, 47: 727, 1927.
44. Henke, K. and Seeger, S. Ueber die Vererbung der myotonischen Dystrophie. Genetischer Beitrag zum Problem der Degeneration. *Ztschr. ges. f. d. Anat. (Abt. 2)*, 13: 371, 1927.
45. Henke, K. and Seeger, S. Über die Vererbung der myotonischen Dystrophie. *Ztschr. f. Konstitutionsl.*, 13: 371, 1928.
46. Penrose, L. S. The problem of anticipation in

pedigrees of dystrophia myotonica. *Ann. Eugenics*, 14: 125, 1948.

47. Talbott, J. H. Periodic paralysis: a clinical syndrome. *Medicine*, 20: 85, 1941.
48. MacLachlan, T. K. Familial periodic paralysis. Description of six cases occurring in three generations of one family. *Brain*, 55: 47, 1932.
49. Oliver, C. P., Ziegler, M. and McQuarrie, I. Hereditary periodic paralysis in a family showing varied manifestations. *Am. J. Dis. Child.*, 68: 308, 1944.
50. Schmidt, A. K. E. Die paroxysmale Lähmung. Berlin, 1919. Julius Springer.
51. Holtzapple, G. E. Periodic paralysis. *J. A. M. A.*, 45: 1224, 1905.
52. Khan, M. Y. Familial periodic paralysis. *Indian M. Gaz.*, 70: 28, 1935.
53. Tyler, F. H., Stephens, F. E., Gunn, F. D. and Perkoff, G. T. Studies in disorders of muscle. VII. Clinical manifestations and inheritance of a type of periodic paralysis without hypopotassemia. *J. Clin. Investigation*, 30: 492, 1951.

Conference on Therapy

Therapeutic Application of Psychosurgery

THESE are stenographic reports, slightly edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: We have with us a visitor from our sister institution uptown, the New York State Psychiatric Institute. Dr. Paul Hoch has made an intensive study of the subject of lobotomy and has accumulated a large experience with it. We are fortunate in having him here today to open the discussion and tell us something about what can be accomplished with this operation and some of the ways in which it is misused.

DR. PAUL HOCH: I should like to discuss the problems of operations for mental disturbances, psychosurgery, from two points of view: first, the kind of patients who are likely to benefit from the operation as well as those not likely to improve or who may even be made worse; and second, the type of surgical operation suited to the particular case. I prefer to use the term leukotomy in connection with this topic even though it is not an accurate expression for there are a number of operations today which are not leukotomies. There is, as you know, the classical form of leukotomy which was first introduced for the treatment of the chronic schizophrenic patient. This operation is still employed in many places, especially in the chronic deteriorated schizophrenic. I may say at once that I am not impressed by the therapeutic results in this type of patient. It depends, of course, on what one expects from the classical frontal lobotomy; if one anticipates total recession of the clinical symptomatology in these patients, one is quite certain to be disappointed. This operation does usually bring about a change. The hallucinations and delusions become less disturbing. The impact of these symptoms on the patient is reduced and in some cases even eliminated. These patients usually behave better. Patients who are disturbed and aggressive usually quiet down but basically the schizophrenic process continues after the operation. The term "administrative improvement" could be applied to this kind of result and it is of considerable importance because a number of these patients become easier to manage. They can be released from institutions for outside care. All in all, these patients are also happier. But the fact remains that complete elimination of the disorder in the chronic deteriorated schizophrenic by frontal lobotomy does not take place in the great majority of cases. They become better behaved schizophrenics than before the operation but they are still schizophrenic.

Because of this experience there has been a tendency to operate on these patients earlier, long before the schizophrenic has developed deterioration. It is clearly not desirable to wait until ten or fifteen years have elapsed after the schizophrenic state has become manifest. But how early to operate is not always easy to decide, for it is difficult to know at times when a schizophrenic has become a patient, when clinical symptomatology has become fixed; and it takes time to discover when the patient has become more or less inflexible and unresponsive to various other therapeutic approaches. We have adopted the policy of operating upon patients who have been continually sick for two to three years and who have in that time failed to respond to other forms of treatment. There are some who operate on them much earlier. I am inclined to disapprove such early application of the operative procedure because other therapeutic measures should always be tried first and the operation should be considered only in those in whom non-operative methods have been tried and have failed, and these methods of treatment must be tested for a sufficiently long period. As I see it, therefore, the place of leukotomy in the treatment of the schizophrenic is not in the period after long years of deterioration and also not in the period

when there is reasonable expectation of influencing the clinical symptomatology by non-operative methods, but at a time when deterioration has not yet taken place and non-surgical treatment has already indicated little likelihood of success. The statistics are clear in indicating that the results with the various operations are better in the well preserved non-deteriorated schizophrenic.

The benefits of the operation are in part related to the clinical symptomatology of the patient. Well preserved patients with paranoid or catatonic states show the most improvement, while in the hebephrenics the response is less conspicuous. Patients with a rather productive symptomatology and those who are usually considered very conspicuously sick are the very ones who are apt to benefit most from the operation; those who are dominated by hallucinations and delusions, who show marked affective tension or who display a great deal of aggression. The results are not satisfactory in the non-responsive and non-productive patients, the apathetic, the indolent, the completely withdrawn. We do not operate upon such patients any longer because some are made even more apathetic and more indolent. In the most general terms, it may be said that overfunctions or hyperfunctions which appear in the clinical symptomatology of the patient can be cut out or reduced by the operation, while underfunctions are not influenced as well, and such patients cannot be brought to a higher level of activity. Of course, it is not an easy matter to decide what in a particular individual constitutes overfunction or underfunction and it requires long study to interpret the signs properly. There are patients with a considerable amount of tension who seem quite withdrawn, patients who appear emotionally blunted and non-responsive in whom a great deal is going on emotionally.

The operation is beneficial in chronic depressions, in chronic manic states and in the chronic involutional depressions which do not respond to other forms of treatment. On the other hand, it has been much less successful with the so-called circular type of patient who has manic or depressive attacks, with intervals free of attacks. This patient shows less response from the operation than the one with straightforward chronic depression or the chronic manic state.

Up to the present time the best results with the operation have been obtained in the chronic neurotic group and the group which we refer to as the pseudoneurotic schizophrenic. We now have a large number of psychoneurotics who had been treated by every means available to psychiatry today, with psychotherapy and psychoanalysis for many years, some up to twenty years, who were then operated upon and their condition reevaluated. Without going into the details of their state before and after operation, I can say that these patients represent the most gratifying results in psychosurgery. Up to about 70 per cent of these patients are relieved of their symptoms. It should be noted that prior to operation these patients were more or less invalided and, of course, the operation was performed only on the most severe cases with very marked obsessive, compulsive and phobic states, on patients who were dominated by their symptoms. After operation these patients can again socialize and many of them resume their occupations. We always insist that the patients of these two groups, as in all other cases, receive adequate psychotherapy or psychoanalysis for several years and that the operation be considered only when these measures have failed. We prefer to operate only on those patients who have failed to respond to treatment by more than one therapist. We make these conditions so stringent because we can afford to wait with the surgical procedure in these cases much longer than in the grossly schizophrenic patients since the danger of deterioration is not great. On the other hand, I believe that one can wait too long in these patients also because, while they do not show the symptomatology of deterioration, there are indications that the results of the operation are better in patients who have been sick for only about five years than in those who have been sick ten or twenty years.

These operations have also been tried in other conditions but experience is still insufficient for definitive statements. In the case of psychopathic personalities, some have been benefited, some unchanged and others have been made worse. Some of these who are not able to control their emotions or actions well show even less control after the operation. On the other hand, the operation usually benefits those patients in whom the psychopathic behavior occurs within the framework of schizophrenia. These patients have to be studied very carefully in order to distinguish those who belong

to the group of genuine psychopaths and those who fit into the group of schizophrenics. The operation has been tried in various kinds of sexual deviates as, for example, in homosexuality. It is not advocated in these. In most of these cases it seems to have no influence on the psychic structure of the patient and some of them are made worse, for a well controlled homosexual sometimes becomes uncontrolled after the operation. On the other hand, patients have been benefited from the operation when deviations of one kind or another occur within the framework of schizophrenia. Again, there is the problem of deciding the particular structure and whether or not the sexual deviation is part of a psychotic picture.

I should now like to devote a few minutes to the other issue, namely, that of selecting the operation best suited to the particular patient. Not long ago one institution would concentrate only on the classical form of lobotomy while another would restrict itself to some other form of operation, but now that a fairly large number of operations have been developed it has become the more general practice to perform the operation likely to give the best results in a particular case. In the case of the chronic deteriorated schizophrenic patient classical lobotomy is the operation that is most successful. This operation should be used only in chronic schizophrenic patients, especially in those with a great deal of aggression, for the further back the cut is made the more aggression and drive are removed; the more anterior the cut the more aggression and drive remain. Again then, classical lobotomy is advised in patients who are too far gone; mental disorganization has reached an advanced degree. In such instances the operation is indicated not so much for the purpose of securing a cure but to modify the patient's clinical symptomatology and especially his conduct. In the well preserved schizophrenic patients, however, we no longer perform classical lobotomy. We no longer use it in the chronic neurotic and the pseudoneurotic group. Classical lobotomy produces side effects which are of little consequence in patients who are already too sick and deteriorated before the operation but are quite important in patients who are well preserved. In the well preserved schizophrenic patients, and in all other patients which I have mentioned, we now prefer the small operations of which there are several at our disposal: so-called median lobotomy, coronal, or lower quadrant lobotomy in which the upper quadrants of the frontal lobe are left intact. The point is that these operations do not call for a full leukotomy but only a partial one on both sides. There has also been some experimenting with operations performed on only one side. There are also the cortical operations like topectomy or undercutting. These less extensive procedures are sufficiently successful in the well preserved schizophrenic, in the chronic depressive manic patients and especially in the chronic neurotic patients. In these it is unnecessary to perform the more extensive classical operation. The small operations are naturally preferred because there is so much less damage to the personality, a factor which is very considerable and has been the subject of much discussion in relation to lobectomy. With the small operations one never sees patients in whom initiative seems to have been cut out, as is the case with classical lobotomy; even so, however, some of the finer intellectual functions like planning, foresight or creativity can be impaired although psychologic tests fail to show such impairment. These impairments are usually not marked and one may consider the fact that in a great many these particular functions may not have been intact even before operation. The less extensive procedures are particularly important for persons whose professional activities require preservation of their symbolic and integrative functions.

There are those who believe that the various operations eliminate certain functions which are localized in particular parts of the brain, in a sense a qualitative operation. Our own experience leads us to a contrary conclusion, that the operation is quantitative. It seems to be irrelevant whether the operation is performed on the upper part of the frontal lobe or on the lower part. We find no evidence to justify the belief that a particular mental symptomatology is related to certain special parts of the frontal lobe. The thing that is difficult to judge in advance for each patient is how much cutting is necessary to influence the patient's symptomatology to avoid removing either too much or too little.

Now I should mention a point which is probably of considerable interest to you, namely, that in all patients the basic structure of the emotional disturbance remains after the operation. This is most conspicuous in schizophrenic patients, much less so in the neurotic patients. It is possible to reactivate some of the structures

and bring back the patient's symptomatology but even though the symptoms can be reactivated qualitatively, their intensiveness is much less and the impact of the symptoms upon the patient is much reduced. The operation therefore accomplishes a great deal in the well preserved patient. It enables the patient to function. I should emphasize again that the operation should be performed only in selected patients as specified, never indiscriminately, and never as the first form of treatment for an emotional disorder.

DR. READER: Thank you, Dr. Hoch. You did not mention the use of lobotomy for intractable pain. Do you have any view about that?

DR. HOCH: I did not want to exceed my time and so I did not take up that subject. We have had a number of patients operated upon for intractable pain. Patients with cancer and intractable pain who are otherwise mentally well organized presented an opportunity for learning more about the effect of the operation itself. When patients are operated upon for mental symptoms, as in schizophrenia, it is difficult to judge how much of the postoperative changes represent modifications of the schizophrenia or actually organic changes resulting from the operation. It is noteworthy that in the mentally well patient with intractable pain the operation results in a state in which the patient perceives the pain but the impact of the pain on the patient is reduced or eliminated, and in some patients the pain experience itself later vanishes. This is very similar to the situation in mental patients in whom the first effect of the operation is to reduce the impact of the symptoms and later the symptoms themselves vanish. For instance, the patients may say: "Yes, the phobic ideas are still coming up," but they are no longer responding to these ideas. They now seem to be able to shut them off and are able to function with them. Later on the idea gradually fades away and the patients become completely symptom-free.

This operation on intractable pain raises the whole question, what is pain? These patients still perceive pain but somehow do not elaborate on it and are free of all the anticipatory fear associated with pain. The reaction of the patients to the knowledge that they have cancer seems to have the same meaning. After the operation they still know that they have cancer and they still perceive the pain associated with it, but what disappears is the anticipatory anxiety that they will soon die from the disorder which was, before operation, a very important part of the patient's pain experience. Those patients with intractable pain who had been using large amounts of morphine or demerol or other drugs need them no longer after the operation, and what is even more interesting is the fact that after this psychosurgical procedure there are no severe withdrawal symptoms such as are usually seen in narcotic addicts under other conditions.

DR. READER: Are there any questions or comments at this point?

VISITOR: Have there been any long term follow-ups on psychoneurotic patients who have had this operation? Also, have any of them undergone psychoanalysis after the operation and with what results?

DR. HOCH: We have cases whom we have followed for about four years and who have remained well. Others have cases which have been followed for longer periods. Very few patients relapse who respond very well to the operation. In those in whom there is a relapse, it usually takes place in the first year after the operation.

As to psychoanalysis after the operation, these patients become much less interested in the analytic procedure than they were before the operation. This can of course be interpreted as signifying that patients who feel well are not very much interested in any form of procedure intended to make them feel well. Self-concern or the anxiety which patients generate play an important role in their symptomatology and it is the impairment of this self-concern which is probably one of the most significant features of the results of the operation. During psychoanalysis after the operation patients usually produce as much material as before and sometimes even more. However, they no longer are as open for interpretations as before. The patient is apt to become somewhat disinterested in psychoanalysis if the operation has been successful. In those in whom the operation has not been very successful and considerable anxiety still remains as, for instance, in phobic patients, the attitude toward the analytic situation is likely to be similar to that before operation. The attitude toward transference also is altered. After operation the patient does not seem much concerned about the transference situation. He usually throws out more uninhibited material, which formerly was rather difficult

for the patient to manage. When the operation has not been fully successful, the transference situation is also changed in the sense that the patient becomes more dependent on the therapist and expects he will do more for him. A more childish attitude can be observed. It is also interesting that some productions, like dreams, occur much less frequently after the operation, which can be interpreted as the result of a reduction in the affective charge.

MR. E. C. SEVRINGHAUS: Has the operation had any influence on diseases which are commonly thought of as psychosomatic?

DR. HOCH: We have not had many of these. We have had the operation performed on a few patients with psychosomatic disorders, and some in whom the psychosomatic disturbance coexisted or alternated with a psychosis. I saw one patient with ulcerative colitis who lost most of his symptoms after a small operation but I know of others in whom the operation was not successful. The operation is not used very much in psychosomatic patients for obvious reasons, and it will be a long time before enough material will accumulate to be able to evaluate the proper place of this operation in psychosomatic patients. Thus far the results have been quite variable. In some the psychosis was influenced but not the psychosomatic disorder, in others the reverse, and in still others both were influenced. The number of patients is still too small for satisfactory conclusions.

DR. READER: I wonder if Dr. Ray would be willing to say something about the risk associated with these operations?

DR. BRONSON S. RAY: The risk is not very great in any of them. The wonder is that more accidents have not occurred. The type of lobotomy that we have used here, and the one which appeals more to me, is that which is performed under direct vision so that we can see and control bleeding; but that is not foolproof either for we have had one death from bleeding. The undercutting jobs would carry a high mortality if they were not performed by skilled people but in their hands the mortality risk is not significantly higher than with the other forms of operation.

DR. READER: As I understand it then, the choice of the operation is not especially important from the standpoint of operative risk.

DR. RAY: I would be more concerned about who is going to do it.

DR. READER: What do you think about unilateral lobotomy?

DR. RAY: We have never used the unilateral operation in psychotic patients. It would be interesting to study the effect of doing one side and then the other. There have been some observations on this point but the story is far from complete. We have done this in lobotomy for pain, dividing one frontal lobe and then the other side at another time, usually because we found that the unilateral lobotomy did not accomplish what we had hoped for.

DR. JOHN P. WEST: Some time ago, during the Salmon lectures, Dr. Fulton developed the point of the qualitative nature of the prefrontal operations. He supported the idea with observations from experiments on the chimpanzee. I wonder what Dr. Ray would have to say about this?

DR. READER: The difference between qualitative and quantitative in relation to these operations is not clear to me.

DR. WEST: The thought involved in the qualitative idea implies that the matter of importance is not how many fibers are severed but just where the cutting is done.

DR. READER: Do you have thoughts on this subject, Dr. Ray?

DR. RAY: I don't think I should be the person to speak about it. I know of Dr. Fulton's experiments. I have heard the arguments for and against the qualitative idea. Our experience here has to do only with complete division of frontal lobe connections bilaterally. My reaction is the same as that of Dr. Hoch: It is a quantitative not a qualitative affair.

DR. HOCH: It is difficult to relate the emotional reactions of the chimpanzee to those of the human and whether one can apply to humans the observations from a particular operation on the brain of a chimpanzee which results, for example, in the disappearance of the rage reaction, is a debatable question. It is highly probable that a particular reaction in the chimpanzee is also not sharply localized and may result from sectioning in various areas of the brain. In any case, the fact is clear that the mental symptomatology of schizophrenia, or of a depression, or of a phobic state is not related to a sharply defined area in the frontal brain of man, such as the superior convolution of the frontal lobe or the orbital surface of the frontal lobe.

DR. READER: Are there any objective ways of

measuring the changes which take place in the patient following these brain operations?

DR. HOCH: In this regard, unfortunately, we face the same basic problems presented by all psychiatry, that of quantitating symptoms which are essentially subjective. In the sense in which quantitation is used in the basic sciences, it does not exist here. Judgments on these patients are based on three kinds of material. There are the psychologic tests which at the present time are much too gross and new tests will have to be devised to detect some of the more subtle changes. There are the patient's own statements which are probably the most important sources of information because the disorder is mostly a subjective one. And thirdly, there is the information one can obtain from observing the patient clinically.

DR. READER: Is the Rorschach test altered?

DR. HOCH: Opinion is divided on this point, some believing that the operation alters the Rorschach test, others being unable to confirm it. I believe, as I have stated, that the psychic structure and psychodynamic organization of the patient are not much changed although the intensity of symptoms is greatly lessened. There is here an important theoretic consideration, namely, the fact that mental symptomatology which was formerly viewed on an essentially qualitative basis will now have to be considered also from the point of view of quantity. It may be necessary to consider that a person becomes sick not because he has a compulsive or phobic idea but because of the extent of it. How well he is able to handle it becomes an important question. When he is not able to handle it he is a psychiatric case; and if he is able to handle it, he is not.

DR. READER: Would you care to make some comments, Dr. Wolff?

DR. HAROLD G. WOLFF: I might say a few words on the subject of pain. Through Dr. Ray it has been possible to analyze experience with these operations performed for intractable pain in forty-four patients. There were two kinds of results: loss of the pain which brought them to the operation in about 10 per cent; and in a larger number, a state in which the patient continued to perceive pain but was no longer concerned about it. Not all in this series were so helped but if we lump them together, from two-thirds to three-fourths of the cases were benefited in these ways. The threshold to pain perception was in no way altered by the operation in any of these patients. We established the intensity of pain and found that in most the pain was of low intensity. Only pain of low intensity was influenced by the operation and since this includes most of the patients with intractable pain, you can see why so many of them were helped. As a result of the operation a few lost the capacity to make discriminations between pains of high and low intensity but this loss of discrimination had no bearing on the other effect of the operation, namely, the ability to be detached and undisturbed by the pain. The result was the same whether the operation was performed on the homolateral or the ipsolateral side of the pain; whether the operation was performed on the dominant or non-dominant lobe. The results are entirely a matter of the amount of brain damaged; the more brain damaged the greater the likelihood of alleviation. It is not a question of one side or both sides but of the amount of brain destroyed. We also noted in a few patients who had had appreciable relief from discomfort that recreation of anxiety induced experimentally or otherwise caused return of the pain.

We have had some experience with drug addiction in these patients after lobotomy and ours does not quite agree with that cited by Dr. Hoch. Our patients did show the usual physiologic manifestations of withdrawal, most striking in the first seventy-two hours, although there was marked falling off of the "craving," of the patients asking for these agents. The picture, of course, is confused immediately after the operation since many of the patients are obtunded at this time. And this probably masks the evidence of craving which is ordinarily present shortly after withdrawal. In a series of patients carefully studied by Abraham Wikler at the Federal Narcotics Farm in Lexington, Kentucky, the physiologic manifestations of withdrawal were found to be present even though the craving or psychological disturbance was absent.

DR. READER: How long does it take a patient to recover from the operation and reach what may be considered the eventual baseline for him?

DR. RAY: That varies a great deal. It is now commonly believed that patients who are operated upon for intractable pain do not do as well as those in whom the operation is performed for a psychosis. They seem to be harder hit and don't seem to come back as quickly. This is probably due to the fact that patients

with intractable pain have debilitating diseases like carcinoma and many of them are in a low nutritional state before operation. This also brings to my mind the point that should be stressed over and over again, namely, that in psychotic patients in whom a lobotomy is performed the eventual outcome is probably dependent on the period of training and rehabilitation after the operation. Perhaps Dr. Hoch would care to comment on this matter.

DR. HOCH: In regard to Dr. Wolff's remark I should simply like again to call attention to the fact that patients with intractable pain who have become addicted to drugs do not call for the drugs after a successful operation and that in our experience so-called physiologic symptoms are also reduced, but not as much as the craving.

In regard to the question as to how long it takes these patients to return to a so-called baseline, there is the interesting fact that the time is shorter the larger the operation. That is so not only in patients with intractable pain but also in mental patients. For example, we have patients in whom a topectomy or undercutting operation was done who showed improvement only after three months, whereas improvement occurs very much more quickly after the classical lobotomy, but of course these patients usually show other disturbances which are not desirable.

On Dr. Ray's point concerning rehabilitation, a great deal has been written. It seems that many of the fancy schemes of rehabilitation of these patients which have been evolved are not really necessary and do not seem to add very much to the course of the patient's recovery. There are two important issues in the after-care of these patients, one, the kind of nursing and two, the kind of environment to which the patient returns after leaving the hospital. The patient should receive adequate nursing attention after the operation and the nurse should be instructed to correct undesirable habit patterns in the patient. A nurse who is familiar with the handling of children does best with this type of patient. She usually has the patience and tolerance which these individuals require. The person assigned to nurse these patients must realize that they are markedly regressed after the operation, that they come back slowly, and that they display many undesirable habit patterns which, however, can be corrected in many instances.

In connection with the environment to which the patient returns after leaving the hospital, one may refer to the comment which Dr. Wolff made, that under conditions of stress, pain which has been relieved by the brain operation may be reactivated. The same is true of the emotionally sick, since the basic structure of the mental disorder is still there. After a highly successful operation the patient usually overcomes the environmental vicissitudes; but in those in whom some emotional disorder remains, the conditions of the environment are of prime importance. One can readily see how these patients might be influenced by an environment of aggression or hostility, and by the various changes in the attitudes of the relatives because the patient has had an operation or displays a pattern of behavior that is different from the one to which they are accustomed.

MR. SEVERINGHAUS: Do morphine and similar drugs have the same kind of effect on pain as a small lobotomy?

DR. HOCH: Some of the drugs do have a similar effect. There has not been a great deal of experimentation with addicting drugs, for understandable reasons. But there is the fact that some years ago depressions were treated with high doses of opium and these proved quite effective. Of course, we don't do that nowadays because of more effective treatments. One can eliminate pain with intravenous sodium amytal but, of course, the effects do not last.

DR. READER: Dr. Wolff, would you like to make a final comment?

DR. WOLFF: You might be interested in this account of a patient with a so-called stress disorder which was reported by Groen. It is the case of a hypertensive in a terminal state. During the war he had been arrested for engaging in black-market activities. When he came out of jail, his wife was estranged. He tried to reinstate relations but she would not have him. The impossibility of improving this relationship was finally settled when he developed lues. In this setting of mounting tension and unwillingness to give up and try again, he developed a striking elevation in blood pressure (230/140), advanced azotemia, eye ground changes and was admitted to the hospital in coma. A leukotomy was performed and after this the patient's point of view about divorce changed so that he was able, through manipulation of his physician, to accept the next step in his life more placidly. Three years later this patient had a blood pressure of about

150/80 and the eye grounds appeared more nearly normal. The result of the operation in this carefully studied case is clearly not due to the damage done to a hypertensive brain center. Rather, the patient had been made more plastic so that he could adopt new attitudes.

SUMMARY

DR. HARRY GOLD: During the past few years attention has been focused on a surgical approach to the treatment of disorders of the mind and this conference was held for the purpose of exploring the kind of results and opinion that have emerged from experience up to the present time. The psychosurgery which was discussed was that of severing the brain in the prefrontal areas. The earliest operation was quite extensive and is referred to as the classical prefrontal lobotomy; but there have since been developed various lesser operations to which the term partial leukotomy or topectomy has been applied and which involve cutting in more limited areas of the brain. Opinion appears to be divided on the question of whether the aim in the operation is to eliminate a specific portion of the brain assumed to be the seat of particular emotions or whether the precise area is of little importance and what counts is the amount of brain in the prefrontal region that is actually eliminated. The consensus in this Conference favored the latter view. Although experience is still too limited for final statements concerning conditions under which these operations should be undertaken and the kind of results that may be expected, there appears to have crystallized opinion on both of these points which were brought out in the discussion and may be summarized here.

The operation is not very effective in the chronic schizophrenic and is applicable only to those mental disorders in which a thorough trial of psychoanalytic measures has failed. It is most successful in those types in which hyperfunction is outstanding in the clinical symptomatology. Patients most responsive to this form of treatment are chronic neurotics and those included under the label of pseudoneurotic schizophrenia, nearly three-quarters of these showing restoration of their ability to work and carry on a reasonably satisfactory social life. Attention was called to the fact that the basic structure of the mental disorder may remain even after the operation in patients who appear to be substantially cured, and that under sufficiently stressful life situations mental symptoms may be reactivated. An interesting conception is suggested by the results of these operations, namely, that mental disorders represent not only a quality but a quantity, and that when the amount is sufficiently reduced by the operation patients may take on the behavior of fairly normal people.

Much emphasis was placed on the need for thorough trial of non-surgical measures in every case of mental disease before the operative procedures are applied. While the best time to turn to psychosurgery is not easy to determine, the view was expressed that long years of active mental disease with deterioration, as in the deteriorated chronic schizophrenic, are not favorable, and the suggestion was offered that the best results are likely to follow leukotomy if there are selected for this operation those patients who are still well preserved and have had three years or so of intensive non-surgical management without avail.

There were many other interesting points elaborated. There was the observation that one of the primary results of the operation is to eliminate the impact of mental symptoms upon the patient himself. The patient may still be aware, for example, of a phobic idea but no longer responds to it. An analogy was drawn between this phenomenon and the pain experience for in these operations performed for intractable pain the patient may still perceive the pain but is no longer disturbed by it. A further analogy was drawn between the effect of the operation and the effect of such drugs as demerol and morphine during the action of which the patient may also continue to be aware of pain but the experience is so altered that the patient no longer reacts with the usual anxiety which contributes the major element of distress in the total pain experience. Thought-provoking suggestions concerning the nature of drug addiction were offered; and although agreement was not complete, the observation was made that after prefrontal lobe operations patients addicted to narcotics no longer show the psychic craving for the drug. It was also pointed out that an important aspect in the ultimate outcome after these operations is the type of nursing care the patient receives and the type of environment to which the patient later returns.

Clinico-pathologic Conference

Persistent Left Pleural Effusion and Localized Osteoporosis

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. R. (No. 217680), was a white spinster seventy-nine years of age, who entered the Barnes Hospital for the first time on December 28, 1952. Because she was disoriented a reliable description of the present illness could not be obtained. It was learned, however, that she had been relatively well until four or five weeks before admission when she developed a cough, which initially was productive only of small amounts of mucoid sputum. Although in the ensuing period the cough became progressively more severe, there was no hemoptysis. Ten days before entry the patient was seen by a physician who found her to be dyspneic. Physical examination at that time revealed that the blood pressure was normal and the heart somewhat enlarged. Fine rales were audible at both lung bases and there was dependent edema. Cardiac enlargement was subsequently confirmed by a roentgenogram of the chest which also showed a questionable left pleural effusion. Five days before the patient entered the hospital she was begun on digitalis; over a period of three days she received 9 cat units after which she began to vomit. The vomitus contained recently ingested food but no blood. Despite the fact that digitalis was discontinued the patient continued to vomit and she became completely disoriented. On the day before hospitalization she was afebrile but her respirations were irregular. The neurologic examination was not remarkable except for obtundity. Physical examination was notable for sticky rales at the right base and the signs of a pleural effusion on the left. Penicillin and streptomycin therapy was instituted and the patient was referred to the Barnes Hospital.

The family history was non-contributory. An adequate past history could not be obtained but apparently the patient had been in good health except for senility and partial deafness.

At the time of admission physical examination revealed the temperature to be 39.2°C., pulse, 80, respirations, 24 and blood pressure 140/80. The patient was an elderly, moderately obese woman who appeared acutely ill. She was mildly dyspneic, disoriented and uncooperative but responded slowly to spoken commands. Her skin was hot, dry and normal in color. There was no significant lymph node enlargement. The pupils were round, regular and equal and reacted normally to light. The fundi could not be adequately visualized. The neck was supple. The chest was emphysematous. Signs of pleural effusion were noted on the left, and medium inspiratory rales were heard over the right lower lung field. Examination of the heart revealed that the left border dullness extended to the left anterior axillary line. The heart sounds were of good quality and the rhythm was regular. No murmurs were heard. Except for voluntary muscle guard abdominal examination was not remarkable. Pelvic and rectal examinations were within normal limits. There was 1 plus ankle edema. Except for the clouded mental status the neurologic examination was normal.

The laboratory data were as follows: red blood cell count, 4,040,000; hemoglobin, 13.4 gm. per cent; white blood cell count, 10,250; differential: 1 per cent eosinophils, 2 per cent band forms, 82 per cent neutrophils, 13 per cent lymphocytes and 2 per cent monocytes. Urinalysis: specific gravity, 1.013; albumin, negative; sugar, negative; sediment, 4 to 6 red blood cells per high-power field. Stool: guaiac negative. Cardiolipin: negative. Blood chemistry: non-protein nitrogen, 50 mg. per cent; sodium, 140 mEq./L; potassium, 3.6 mEq./L; carbon

dioxide combining power, 27.8 mEq./L; chloride, 102 mEq./L. Roentgenogram of the chest: There was generalized cardiac enlargement, left pleural effusion, pulmonary vascular congestion; small spotty areas of decreased density were noted in the left clavicle, acromion and proximal humerus which were thought to represent osteoporosis. Electrocardiogram: Abnormal form of ventricular complex and digitalis effect.

Penicillin and streptomycin administration were continued and the patient became afebrile by the fifth hospital day. Although she became somewhat less obtunded, she remained disoriented. Vomiting ceased soon after admission but although she took fluids adequately she refused solid food. On the fifth hospital day digitalis therapy was again started in a dose of 1 cat unit daily.

Despite the clinical improvement a subsequent chest roentgenogram revealed progressive increase in the left pleural effusion. On the tenth hospital day 350 cc. of straw-colored fluid were removed from the left pleural cavity and on the following day a thoracentesis yielded 800 cc. of similar fluid. Both bacteriologic and cytologic studies of these fluids were negative. The specific gravity was not recorded. Although penicillin and streptomycin had been continued, the patient's temperature rose on the eleventh hospital day and throughout the remainder of her hospital course remained elevated. Concomitantly with the development of fever the pulse rate was observed to slow progressively, remaining regular at 46 to 60 per minute. Digitalis was discontinued temporarily and the pulse slowly returned to normal.

On the eleventh day the red blood cell count was 5,400,000, hemoglobin 14.4 gm. per cent, white blood cell count 20,600; the differential count showed 1 per cent eosinophils, 3 per cent band forms, 79 per cent neutrophils, 15 per cent lymphocytes and 2 per cent monocytes. The following day the white blood cell count was 10,400, the differential showing 6 per cent band forms, 59 per cent neutrophils, 18 per cent lymphocytes and 8 per cent monocytes. The non-protein nitrogen remained within normal limits.

On the fifteenth hospital day the patient was found to have slight stiffness of the neck and a lumbar puncture was performed. The spinal fluid was clear and the initial pressure was normal. On examination there were 6 mononuclear cells; the protein was 63 mg. per cent, sugar 86 mg. per cent, chloride 118 mEq./L; and the colloidal gold curve, Wassermann and culture were all negative. On the following day the patient had two generalized convulsions during which her head and eyes turned to the left. She subsequently became comatose. A neurologist saw the patient in consultation and noted the presence of a left facial paresis. Her respirations became irregular and oxygen therapy was begun. A white blood cell count at this time was 8,750 with a differential showing 6 per cent band forms, 80 per cent neutrophils, 8 per cent lymphocytes and 6 per cent monocytes. Repeat examination of the urine was of interest because of the presence of 10 to 15 white blood cells per high-power field; culture showed a heavy growth of Candida stellatoidea.

The patient's temperature ranged between 38 and 40°C. Although the amount of fluid in the left pleural cavity gradually increased, her mental status improved and by the eighteenth hospital day she was again able to respond to her name. She refused to eat, however, and gastric tube feedings were given. Rales were heard intermittently over both lungs. The patient coughed up small amounts of purulent sputum. On the twenty-first day her white blood cell count was 17,300, the differential showing 7 per cent myeloblasts, 2 per cent myelocytes, 3 per cent band forms, 70 per cent neutrophils, 17 per cent lymphocytes and 1 per cent monocytes.

During the fourth week of hospitalization the patient's sputum was noted to be blood streaked but the physical findings remained essentially unchanged from those previously noted. No evidence of peripheral thrombophlebitis could be found and a pleural friction rub did not develop. Another white blood cell count showed some decrease, the total having fallen to 13,050. The differential count revealed 3 per cent eosinophils, 18 per cent band forms, 53 per cent neutrophils, 22 per cent lymphocytes and 4 per cent monocytes. Two days after the onset of hemoptysis the signs of pleural effusion were noted not only on the left but on the right as well. A portable chest roentgenogram was obtained and confirmed the presence of bilateral effusions. The patient lapsed into coma. Her urinary output decreased slightly and the non-protein nitrogen rose to 55 mg. per cent. Despite continued digitalis and salt restriction, massive edema developed. On January 27, 1952, she gasped suddenly and expired.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The problems in this case are amplified by reason of the fact that an adequate history could not be obtained. We are told that the patient had enjoyed good health until her present illness but even that information is probably open to question. Presumably the present illness began only four to five weeks prior to her admission to the Barnes Hospital and was characterized by the symptoms outlined in the protocol. After the patient was admitted to the hospital the most prominent findings were cardiac enlargement and a left pleural effusion. There was initially a favorable response to antibiotics but subsequently the patient became febrile. During most of her hospital stay she had a leukocytosis. About two weeks after entry two generalized convulsions occurred and at this time a neurologic consultant observed that the patient had a left facial paresis. In the fourth week her sputum became blood-tinged for the first time and terminally she developed azotemia and edema. Before we begin our general discussion, Dr. Elliott, would you make some comment on the roentgenographic findings?

DR. GLADDEN V. ELLIOTT: I have reviewed the radiographic examinations of the chest including the film taken before the patient was admitted to the hospital. The latter revealed an opacity over the left lower lung field which, in view of later developments, must have represented a pleural effusion. Subsequently left pleural effusion was noted on all examinations. Although the extent of the effusion decreased after the two thoracenteses, it recurred very promptly and was most extensive on the last film obtained, just prior to death. The underlying pulmonary parenchyma was never adequately visualized, and consequently intrinsic pulmonary disease cannot be excluded. The patient exhibited persistent cardiac enlargement and aortic tortuosity. The pulmonary vascular markings indicated some passive congestion on the last two examinations. Finally, areas of mottled, irregular radiolucencies in the proximal portion of the left humeral diaphysis persisted throughout the period of observation. In the absence of a history of trauma or localized arthritis which could account for localized disuse atrophy, one must seriously consider these lesions to represent osteolytic bony metastases. No information regarding the possible site of a primary tumor is available unless the persistent left pleural effusion was related to a malignant lesion; the effusion probably could have been due merely to cardiac failure.

DR. MOORE: One of the interesting points in this history was the fact that the patient developed signs of digitalis intoxication after having received only a relatively small amount of the drug. Dr. Massie, you will recall that she began to vomit after receiving 9 cat units of digitalis and then was given none for two days prior to admission and for five days after admission. Nonetheless, although she then was given the drug only in a maintenance dose, within a week or so her pulse rate fell to a relatively low level and did not return to a normal value until after digitalis had been discontinued.

DR. EDWARD MASSIE: May I ask over what period of time the original 9 cat units were given while the patient was still at home?

DR. MICHAEL M. KARL: She received that amount over a three-day period.

DR. MASSIE: That is certainly a conservative dosage schedule; I would agree that the patient's response was distinctly unusual considering the small dose. In very old patients, however, digitalization must be approached with caution and even trepidation. Most of them have a considerable amount of vagotonia, and our experience in the Heart Station leads us to believe that most of them have more sinus arrhythmia than do younger patients. Because vagotonia is so pronounced in old people, digitalis in small amounts may produce sinoauricular block or even nodal escape. The sudden vomiting which this patient exhibited could have been due to digitalis, but in view of the fact that she also became disoriented I wonder if there were not other factors involved. One should point out, of course, the fact that this patient almost certainly had arteriosclerotic coronary artery disease. The amount of involvement was probably not too extensive, despite the patient's age, because the electrocardiogram was not strikingly abnormal. On the other hand, there was a significant degree of cardiac enlargement but I doubt that cardiac failure was of great importance in the illness. In summary, therefore, I would implicate factors other than those involving the heart.

DR. MOORE: As you followed this patient, Dr. Karl, during her stay in the hospital did you come to the conclusion that she was or was not in heart failure?

DR. KARL: When we first saw her she had

rales at both lung bases, hepatomegaly and dependent edema. Those findings plus the cardiac enlargement suggested to us that she did have cardiac failure. However, there were several features that were rather disturbing. First, the marked pleural effusion was entirely out of proportion to the other manifestations of failure. Second, as Dr. Massie has suggested, the sudden onset of vomiting was not what one would have suspected from overdigitalization *per se*. It came on abruptly and was almost projectile in nature, and with it she became obtunded. I think in answer to your question that she did have some degree of congestive failure, but I agree with Dr. Massie that it was not a major part of her illness.

DR. MOORE: Dr. Karl, do you think she was ever completely digitalized?

DR. KARL: Are you referring to the period prior to hospitalization?

DR. MOORE: Not necessarily. It would be helpful to know whether the persistent effusion and the edema were due to cardiac failure; if the patient had been completely digitalized, cardiac failure would perhaps be a less likely explanation of these findings.

DR. KARL: Initially she made a rather satisfactory response to digitalis in that both edema and hepatomegaly decreased, but I cannot be certain that digitalization was ever complete.

DR. BERNARD A. BERCU: During the period late in her course when she was developing edema were her neck veins distended?

DR. MOORE: No, they were not. Taking all the data at hand, it would seem reasonable to conclude that the patient did have some degree of failure but we cannot be certain exactly what part it played. Dr. Massie, at least, thinks that cardiac failure was never of great import.

Let us consider now another important problem, that relating to the localized osteoporosis. Dr. Daughaday, do you agree with Dr. Elliott that localized areas of decreased bone density in the shoulder region are usually not manifestations of osteoporosis.

DR. WILLIAM DAUGHADAY: In general I would. I am somewhat troubled by the fact that the shoulders of older people are often subject to prolonged limitation of motion. For example, in this case, the patient may have had a fracture necessitating immobilization for a long time and resulting in localized osteoporosis. Of course, the history did not give any indication of such an event but we have all questioned its reliability.

DR. MOORE: Dr. Karl, can you shed any light on this phase of the problem?

DR. KARL: This woman did have arthritis, probably both rheumatoid and hypertrophic osteoarthritis, which may have played some part in limiting motion in her shoulders.

DR. MOORE: Were you conscious of the fact that the limitation of motion was greater on the left than on the right?

DR. KARL: No, I was not.

DR. MOORE: Dr. Elliott, is it possible to differentiate between localized osteoporosis and metastatic carcinoma?

DR. ELLIOTT: I do not think accurate differentiation is always possible. As I have previously indicated, this patient had a mottled area of radiolucency limited to the proximal portion of the left humerus. Because of the asymmetry and lack of change elsewhere, I would doubt that these changes represent osteoporosis of the senile type. If indeed she had osteoporosis and not metastatic carcinoma, the osteoporosis must have been due to disuse of the left upper extremity.

DR. DAUGHADAY: One could be quite sure that these changes were not those of senile osteoporosis *per se*. The patient had no collapsed vertebrae whereas any patient with osteoporosis in the peripheral long bones certainly ought to have the "fish-spine" described by Albright. The differential diagnosis, therefore, lies between localized bone atrophy due to disuse and metastatic carcinoma.

DR. MOORE: Before we pursue the question of metastatic carcinoma let us consider the hematologic findings which suggest a leukemoid reaction. First, I would like to make a few general comments about the differential counts reported in the protocol. Miss Minnich and I reviewed all of the slides which were obtained on the patient and which had been saved in the Clinical Microscopy Laboratory. Our interpretation agrees essentially with that recorded by the laboratory. The largest number of young cells present was noted on the twenty-first day as described in the protocol. However, in the differential counts both before and after that particular one we consistently found some young cells, including at least 1 nucleated red blood cell, a number of myelocytes, young monocytes and distinct, typical young lymphocytes. We saw no plasma cells. One could say then that the differential counts were in keeping with a rather broad picture of immaturity. Dr. Reinhard,

would you comment on these findings as they bear on the diagnosis in this case?

DR. EDWARD H. REINHARD: Changes from the normal such as were noted here could occur in any one of a number of systemic diseases or in disease of the bone marrow. It is difficult to go much further than to indicate that this type of hematologic response is compatible with infection, with tuberculosis of the disseminated type, or with carcinoma involving the bone marrow.

DR. MOORE: Could the changes described in the left humerus be those of tuberculosis, Dr. Elliott?

DR. ELLIOTT: That would be most unlikely. The involvement was principally in the diaphyseal portion of the humerus, whereas when tuberculosis occurs in bone it usually appears in the epiphyseal portion. Although the joint may be spared initially, later in the course of the disease it, too, becomes involved. With this type of bone tuberculosis there is rarely extensive involvement of the diaphysis. A second form of bone involvement in tuberculosis, that due to hematogenous spread, may begin in the diaphysis, but usually gives rise to sclerosis rather than to osteoporosis such as was seen here.

DR. MOORE: A few years ago it was reported that nucleated red cells could be found in the peripheral blood of individuals with cardiac decompensation. Does an outpouring of young white cells occur in cardiac decompensation in the same way? In other words, could the leukemoid reaction noted here be due to that factor alone?

DR. MASSIE: I know about the report to which you refer. The incidence of nucleated red cells in the peripheral blood in cardiac decompensation must be extremely rare. I know of a rather large series of patients with profound heart failure studied carefully for this phenomenon, and in no instance were nucleated red cells found. I am not aware that cardiac decompensation *per se* can cause a leukemoid reaction.

DR. MOORE: This woman probably had a pulmonary infection, Dr. Wood, at least to some degree. The possibility that the peripheral blood changes could be explained on that basis should be mentioned although I myself think it would be unusual to find immature lymphocytes and monocytes under such circumstances. I would have expected a shift to younger forms in the granulocytic series. Do you agree with me in this regard?

DR. W. BARRY WOOD, JR.: Yes, I do.

DR. MOORE: I should like now to turn to the consideration of the fourth problem, that of the neurologic complications. Dr. Levy, you saw this lady in consultation and I believe you saw her during one of the convulsions. Dr. Karl has already mentioned the fact that her vomiting was projectile in type. May her obtunded mental state, at least to some extent, have been due to a cerebral lesion? Would you give us your opinion of her neurologic status?

DR. IRWIN LEVY: Actually I saw this patient several months before her admission to the hospital. At that time she showed evidence of rather profound senile deterioration. She was disoriented in terms of both time and place, and had difficulty in finding her way around. She was quite forgetful. When she was admitted to the hospital, it seemed to me that the neurologic findings could be explained on the following basis: that the circulatory changes had already compromised the nervous tissue to a large degree and it was further compromised by the hypoxia incident to pulmonary infection. A clinical picture such as this one is not at all uncommon under such circumstances. The convulsions she had were focal in character arising from the right hemisphere, and the residual weakness was related to the convulsion. This probably was in the nature of a Todd's paralysis. I did not think that there was evidence of a space-occupying lesion; the spinal fluid examination just prior to the convulsion was not abnormal. Finally, projectile vomiting is not necessarily associated with central nervous system lesions; conversely, vomiting which is non-projectile may be.

DR. MOORE: On the basis of Dr. Levy's comments it is conceivable that the entire clinical picture presented by this woman could be explained by cardiac failure due to arteriosclerotic coronary artery disease plus generalized arteriosclerosis and pneumonitis.

DR. WOOD: May we ask about the pleural fluid. Ideally we would like to have more information than we have. The fluid was described as straw-colored and we have been told that the bacteriologic and cytologic studies were negative. The specific gravity was not determined, but do we know whether it clotted, and if not, what kind of cells it contained?

DR. MOORE: I'm sorry, Dr. Wood, but the only information we have came from the Surgical Pathology Laboratory report. That

report stated that there were comparatively few cells in the block, but mention is made of the fact that the specific gravity could not be determined because the fluid had clotted. Do you think that these other data would be helpful in terms of differential diagnosis?

DR. WOOD: I would like to refer that question to Dr. Goldman.

DR. ALFRED GOLDMAN: I think they would be very helpful. As a matter of fact I was going to ask the same questions Dr. Wood did. If the specific gravity had been very low, one would have considered the fluid a transudate. On the other hand, if the specific gravity was above 1.020 or 1.021 and had a high total protein, it would be much more in keeping with an inflammatory process. It is of some interest that in a large series of cases I studied in which pleural effusion complicated tumors, the specific gravity in the majority ranged between 1.015 and 1.018 although there were some exceptions.

DR. MOORE: This problem is a practical one which arises frequently. Very often the specific gravity of pleural or ascitic fluid is not determined. I wonder whether a hydrometer should not be incorporated in all thoracentesis and paracentesis sets so that the specific gravity could be determined at the bedside.

DR. WOOD: As has already been stated, if we knew the specific gravity of the pleural fluid in this case we might be able to tell whether the patient had cardiac failure only or whether there were some other disease process in the left pleural cavity. I think many of us suspect that something else was going on. The fact that the fluid clotted may be of some help for the pleural fluid from patients with congestive failure often does not clot. Isn't that correct, Dr. Goldman?

DR. GOLDMAN: Yes, frequently the transudates arising as a result of congestive failure are of extremely low specific gravity.

DR. MOORE: On the basis of this inference, Dr. Wood, do you want to make a diagnosis of carcinoma?

DR. WOOD: I think that possibility is a real one, Dr. Moore. Either this patient had a bronchogenic carcinoma with involvement of the pleura, bone and brain or she had only congestive heart failure with bronchopneumonia and cerebral arteriosclerosis. It is pertinent that carcinoma of the bronchus often metastasizes to the brain. I don't think definitive differentiation is possible with the information at hand but I would favor carcinoma. Dr. Elliott and Dr. Daughaday have already pointed out that the localized bone lesions are difficult to explain unless they arose on the basis of disuse or were due to metastatic tumor. The leukemoid reaction, incidentally, is compatible with disseminated carcinoma.

DR. MOORE: We have recently had several cases in which chest films were interpreted as suggesting lymphangitic spread of carcinoma and in each one of them this interpretation was wrong. I am sure Dr. Elliott considered that possibility here and probably did not mention it because of our recent experience. Dr. Goldman, would you comment on this point?

DR. GOLDMAN: It is difficult to be certain about lymphangitic carcinomatosis on x-ray films. As Dr. Elliott stated in discussing the original film, the pleural effusion obliterated most of the left lung but the right side was relatively clear. It is impossible to know whether a lesion in the left lower lobe was obscured by the fluid but certainly bronchogenic carcinoma came to my mind. The fever and the sputum could have been explained on the basis of secondary infection, either pneumonitis or abscess. As has been suggested, carcinoma would also be compatible with the occurrence of convulsions due to metastases. One cannot rule tuberculosis out completely although I think it is quite unlikely here.

DR. MOORE: Do you have any comment, Dr. Glaser?

DR. ROBERT J. GLASER: The case which has been made for carcinoma is a rather strong one. In regard to the problem of cardiac failure when unilateral pleural effusion occurs in congestive failure, it is much more common on the right than on the left side. This point perhaps favors some other cause such as carcinoma.

DR. KARL: It has always been my impression, as apparently it is Dr. Glaser's, that left-sided pleural effusion alone in congestive failure is uncommon. When this patient was admitted to the hospital this point came up for discussion with the house staff and I took the occasion to look it up in the literature. I found a report in the British Heart Journal in which right-sided pleural effusions on the basis of congestive failure occurred in sixty-eight cases whereas left-sided pleural effusions were seen in forty-two.[1] On the basis of that particular report one

[1] BEDFORD, D. E. and LORIBOND, J. L. Hydrothorax in heart failure. *Brit. Heart J.*, 3: 93, 1941.

would assume that unilateral left-sided effusion is not especially uncommon. On the other hand, White studied a series of fifty cases of heart failure with unilateral effusions and found the left side involved in only four.[2] Further, all four of the patients had either pulmonary infarction on the left or an obliterated pleural cavity on the right. There must be considerable variation, but in general unilateral pleural effusion due to cardiac failure probably is much more common on the right.

DR. MASSIE: I would agree with both Dr. Glaser and Dr. Karl. Whenever cardiac failure is associated with only a left pleural effusion one should suspect coincidental pulmonary disease. In the present case, therefore, in addition to carcinoma, one should consider some other inflammatory pulmonary disease.

DR. MOORE: Do you mean, for example, pneumonia?

DR. MASSIE: Yes, pneumonia with pleural effusion resulting therefrom.

DR. WOOD: Pleural effusion complicating pneumonia would be a reasonable explanation; an abscess could also be accompanied by a pleural effusion. I don't think that pulmonary suppuration involving the left lower lobe can be ruled out.

DR. ALBERT I. MENDELOFF: In trying to decide whether or not this patient had carcinoma or a suppurative lesion of the left lung, one comes back to the question of the significance of the osteoporotic area in the left humerus. The patient could well have had a lung abscess with a metastatic brain abscess but an abscess in the humerus would be most unlikely.

DR. MOORE: Assuming this patient did have carcinoma, would you care to suggest any primary site other than the bronchus?

DR. MENDELOFF: One should consider carcinoma of the thyroid, of the stomach or of the breast but there was no evidence to incriminate any of these organs.

DR. MOORE: In other words, you would agree that if she had a carcinoma, bronchogenic carcinoma is the most likely one.

DR. MENDELOFF: Yes.

DR. MOORE: What is your opinion in this regard, Dr. Flance?

DR. I. JEROME FLANCE: I would definitely favor carcinoma but would consider pulmonary suppuration an alternative possibility.

DR. BERCU: Carcinoma of the bronchus not uncommonly involves the heart—both the pericardium and the myocardium. Perhaps there was such involvement here.

DR. MOORE: There seem to be two major possibilities, first, that the patient had cardiac failure, pneumonitis, perhaps a lung abscess involving the left lower lobe and advanced cerebral arteriosclerosis; or second, that she had a carcinoma, probably of the bronchus, which metastasized to the brain and humerus. Although I do not know the pathologic findings, I do have added information. I was told by Dr. Robert Moore prior to the conference that at the time of autopsy a definitive gross diagnosis could not be made. Assuming, therefore, that the diagnosis had to be based on microscopic study I would personally favor a bronchogenic carcinoma.

Clinical Diagnoses: Cardiac failure; pneumonitis with ? lung abscess; cerebral arteriosclerosis; carcinoma of the bronchus with metastases to the brain.

PATHOLOGIC DISCUSSION

DR. JOHN M. KISSANE: At the time of autopsy there was a moderate degree of generalized subcutaneous edema. The abdominal cavity contained 100 ml., the right pleural cavity 100 ml. and the left pleural cavity 1,500 ml. of clear, yellow fluid with a specific gravity of 1.010. The lungs together weighed 1,200 gm. The right lung was firm, dark and red. The cut surface was moist and exuded bloody fluid. The left lung, on the side of the larger effusion, was markedly compressed. The bronchi, particularly those in the upper lobe of the left lung, contained blood-stained mucus. A small tertiary bronchus to the apical segment of the left upper lobe led into a 1 by 1.5 cm. ill-defined mass over which the pleura was slightly drawn in. On cut section this mass was composed of a number of small nodules of white, rather soft, plastic tissue arranged about a minute central cavity. The tracheobronchial lymph nodes were hard and the cut surfaces black and fibrous. A few of the nodes contained a fine rim of white tissue around the periphery.

The heart was enlarged to 450 gm. The abdominal viscera showed evidence of slight congestion but no significant lesions. The brain was normal upon external examination. Multi-

[2] WHITE, P. D., AUGUST, S. and MICHIE, C. R. Hydrothorax in congestive failure. *Am. J. M. Sc.*, 214. 243, 1947.

ple step sections showed an area of pale softening 1.5 cm. in diameter in the anterior portion of the right hypothalamus, a similar area of the same size in the inferior gyrus of the left temporal lobe and smaller areas subcortically in the frontal lobes. The latter were brown, spherical areas of softening, the borders of which were a poorly defined capsule of granular, yellow-white tissue.

DR. ROBERT A. MOORE: At the time of the gross examination no particularly impressive lesions were recognized. The first microscopic section (Fig. 1) is from the cystic tissue in the posterior portion of the upper lobe of the left lung. In the center there is a bronchus with total destruction of its walls and replacement by irregular anaplastic cells which extend out into surrounding tissues. In Figure 2, from the same bronchus under higher power, the anaplastic character of these cells replacing the wall of this bronchus is clearly seen. This patient had a primary carcinoma of the peripheral part of the lung, so situated next to the mediastinum and behind the hilum as to be undetectable in the chest film. Other sections from the lower lobe of the left lung showed small nodular metastases of this tumor within the pulmonary parenchyma. Otherwise the left lung, as shown in Figure 3, is remarkably clear except for some congestion and edema. There is a small amount of anthracosilicosis, but no evidence of pneumonia at the time of death or of focal organization such as might be expected if there had been pneumonia in this lung some two or three weeks before.

The foci of softening in the brain (Fig. 4) show filling of the Virchow-Robin spaces by the moderately tall columnar carcinoma cells arranged in glandular forms. Necrosis, encephalomalacia which was cystic in some of the older foci, and gliosis of the adjacent brain tissue are present in these regions whose blood vessels have been surrounded by carcinoma. The destructive lesion in the anterior hypothalamus is so located it could well account for hyperpyrexia. In Figure 5 you will see the remarkable growth of this tumor into and lining the pia mater and from there downward into the brain substance along the Virchow-Robin spaces surrounding the blood vessels. Random sections taken from various regions of the brain did not show a universal seeding as might have almost been expected from this section. The meninges were invaded apparently only in the latest metastases where the tumor formed nodules and also produced associated encephalomalacia. The only other site besides the tracheobronchial lymph nodes to which this tumor was found to have spread was the adrenal, where the sinusoids were lined by carcinoma cells. This patient, therefore, had carcinoma at the periphery of the lung in the lower part of the left upper lobe posteriorly with metastases to tracheobronchial lymph nodes, to the lower lobe of the same lung, to the brain and to the adrenals.

There were a number of incidental microscopic lesions in this case. This patient had chronic interstitial pancreatitis with an increase in connective tissue, a slight cellular infiltration and dilatation of some of the intercalated ducts and inspissation of secretion in them, perhaps related to terminal elevation of the non-protein nitrogen. In the liver there was a very definite increase in the amount of portal connective tissue with extension into the lobules and isolation of individual liver cells. The liver cells were markedly irregular, often multinucleate, and had large, bizarre, hyperchromatic nuclei. There was no chronic passive congestion, but the central zones did show dilatation of the sinusoids and distention with blood indicative of a degree of acute passive congestion.

There was arteriolosclerosis throughout the tissues and Figure 6 illustrates the very slight thickening of the basement membrane present in all the glomerular capillaries. I find it quite difficult to evaluate just how much passive congestion or cardiac decompensation was present in this patient. There was a large heart, small amounts of fluid in the peritoneal and right pleural cavities, and a much larger hydrothorax on the left. The presence of the tumor against the pleura could certainly have accounted for a good deal of the fluid on that side. I, therefore, come to the conclusion that cardiac failure was a minor feature in this case. It certainly cannot be denied that there was some evidence of such in the liver and spleen and there were small amounts of fluid in some serous cavities that could not otherwise be accounted for except on the basis of cardiac failure. In addition, there was focal interstitial myocarditis as is illustrated in Figure 7. Its significance is very difficult to evaluate. It might be a reaction to metastatic tumor, but we are unable to identify individual tumor cells. It is simply an infiltration of lymphocytes and a few plasma cells and mononuclear cells into the interstitial

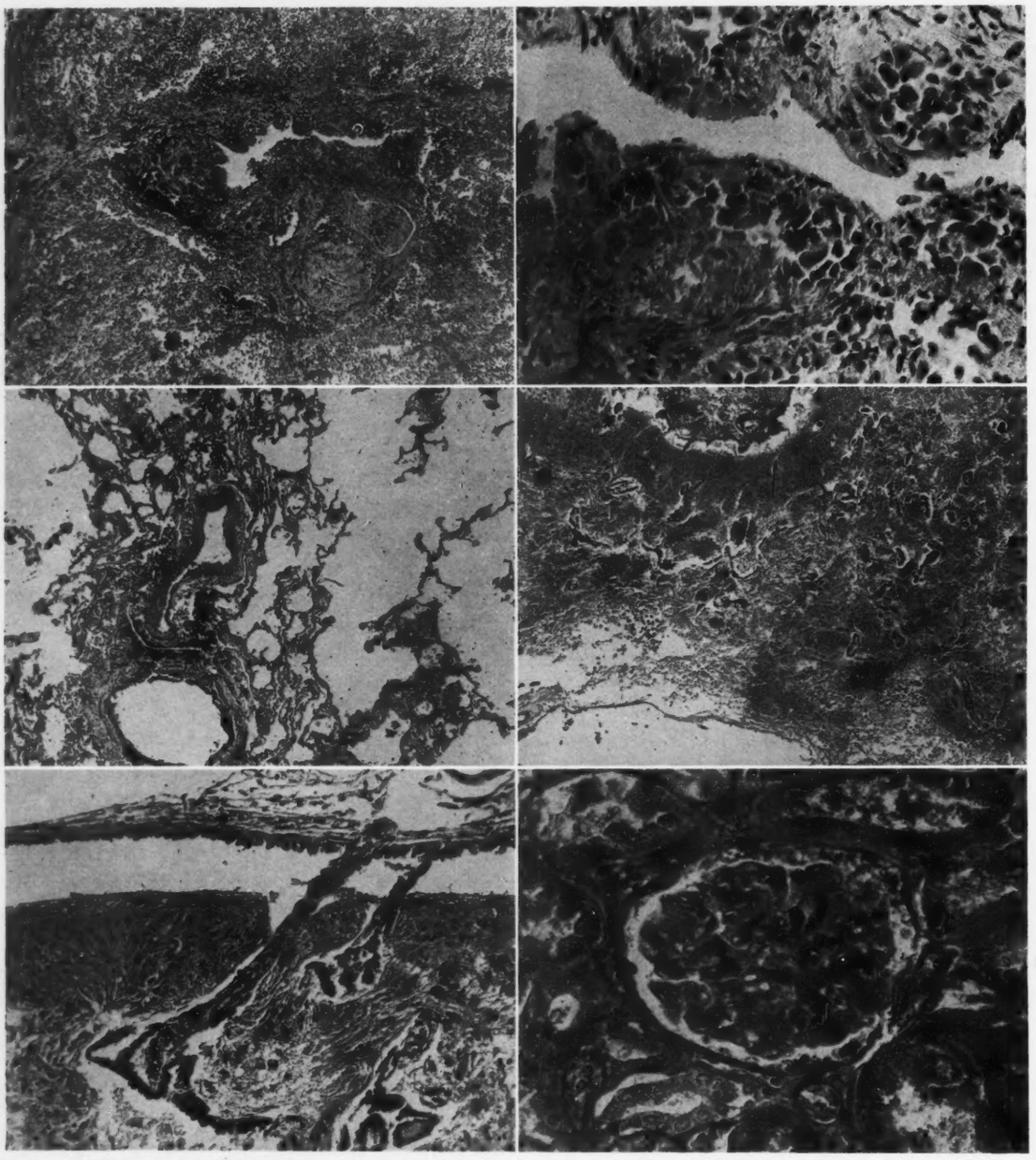


FIG. 1. A bronchus completely invaded by carcinoma in the mass of tumor of the upper lobe of the left lung.

FIG. 2. Undifferentiated carcinoma of the bronchus lining the lumen of a small bronchus, at higher power.

FIG. 3. Lower lobe of the left lung showing congestion but no evidence of present or immediately resolved pneumonia.

FIG. 4. A focus of encephalomalacia in the brain with gliosis and cystic formation adjacent to involvement of the Virchow-Robin spaces by metastatic carcinoma.

FIG. 5. Metastatic carcinoma invading the Virchow-Robin spaces and lining the pia arachnoid over one of the nodules of metastatic tumor.

FIG. 6. Thickening of the basement membrane of capillaries of the renal glomeruli as an expression of generalized arteriolosclerosis.

tissue of the myocardium. It may have played a slight role in the cardiac failure, or it may have been more a reflection of the patient's general physical status. The morphologic changes which occur in the heart with digitalis intoxication, so far as I know from experimental animals and a few human cases, are not characterized by this type of lesion.

Unfortunately, we did not examine the left humerus, so I cannot tell you what the lesion was in that bone. A section of the bone marrow showed a slight degree of hyperplasia of all elements but certainly nothing resembling leukemia.

This case cannot be very satisfactorily summarized. There was a rather small tumor in the periphery of the lung that gave rise to at least two major metastases in the brain which in turn accounted for some of the signs and symptoms but not the mode of exitus. The other metastases were of no importance at the time of the patient's death. She also had cardiovascular renal disease, but there was not too much evidence that it was a major factor in her death. The combination of the effects of these conditions, however, might explain some of the events. The large amount of fluid of low specific gravity in the left chest might well represent the effect of tumor under a pleural surface that had altered properties of absorption and permeability due to co-existent cardiac failure. The patient apparently had two major diseases, neither one of them of such a grade, severity or type as is ordinarily seen in a patient dead of one or the other.

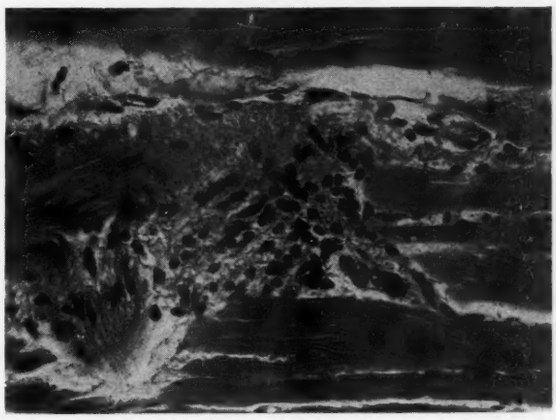


FIG. 7. A collection of lymphocytes and plasma cells in the interstitial tissue of the heart constituting an interstitial myocarditis of unknown significance in relation to the patient's course.

Final Anatomic Diagnoses: Peripheral bronchogenic carcinoma with metastases in the tracheobronchial lymph nodes, left lung, adrenal and brain; metastatic carcinoma with adjacent encephalomalacia in the anterior hypothalamus; hydrothorax; arteriolosclerosis, generalized, slight; hypertrophy of the heart; congestion of the liver and spleen, slight.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Report

Mediastinal Hemorrhage Secondary to Uremia*

NATHAN BROWN, M.D., A. J. TOMSYKOSKI, M.D. *and* RICHARD C. STEVENS, M.D.
Binghamton, New York

THE authors would like to present an unusual case of thrombosis of the anterior mediastinal veins with interstitial hemorrhage secondary to chronic glomerulonephritis and uremia. No mention of this complication can be found in the literature. This patient had other complications arising during the period of her treatment but these will not be dealt with extensively and are mentioned only in passing.

CASE REPORT

G. E., a thirty-five year-old white female, was first seen by one of us (N. B.) on August 23, 1951, with the complaint that she had not felt well intermittently since the birth of her baby three years previously. She had felt worse in the preceding three weeks with frequent vomiting, bloody diarrhea, occasional epistaxis, palpitation and dyspnea. It was difficult to obtain an accurate history because the patient was drowsy and her memory was defective. Past medical history revealed that she was admitted to the Binghamton City Hospital and delivered a baby boy on December 15, 1943. At that time her urine was negative and her blood pressure ranged between 95–110/60–0. She was readmitted November 18, 1946, after a complete abortion at home; plasma was given and she was discharged three days later. The blood pressure at the time of that admission was 102/74. She again became pregnant and visited her gynecologist on September 29, 1949, at which time her weight was 194½ pounds, the blood pressure 130/78, Wassermann reaction negative and Rh-factor positive. Urinalysis revealed a slight trace of albumin and sugar. She was placed on a salt-free diet and nutritive capsules and on October 13, 1949, her blood pressure was 114/80 and the urine was negative for albumin and sugar. Her blood pressure remained normal throughout her pregnancy.

Physical examination on August 23, 1951, revealed an obese, very pale, drowsy white female with a uremic odor to her breath. Her weight was 213 pounds, height 5 feet 3½ inches, respiratory rate 24 and blood pressure 170/110. The remainder of the physical examination was otherwise negative except for an old absorbed hemorrhage in the left fundus. The patient was admitted to the Binghamton City Hospital the following day and placed on a 1200 calorie, low-salt diet. She continued to have profuse, non-bloody diarrhea and complained of severe weakness. Her blood pressure ranged between 160 and 170 systolic and 90 and 100 diastolic. Laboratory work on admission revealed a red blood cell count of 3.21 million cells per cu. ml., hemoglobin of 9 gm. and a white blood cell count of 5,650 cells per cu. ml. with a normal differential count. Catheterized urinalysis revealed a specific gravity of 1.012, albumin 150 mg. per cent, 4 to 6 white cells and 2 to 4 red cells per high power field and numerous granular casts. The non-protein nitrogen was 99 mg. per cent, the blood cholesterol 324 mg. per cent and the serum proteins were reported as 6.5 gm. per cent with an albumin of 3.6 gm. per cent and a globulin of 2.9 gm. per cent. Three days following admission the non-protein nitrogen was reported as 104 mg. per cent and the next day the blood urea nitrogen was reported as 67 mg. per cent. A bone marrow study showed depression of the erythrocytic series but no arrest of maturation while the myelocytic series showed a leukemoid reaction compatible with some prolonged toxicity. A barium enema was reported as negative and a phenolsulfonphthalein test showed no excretion of dye.

The patient was discharged from the hospital against advice on September 1, 1951, but she returned to the attending physician's office ten days later complaining of severe weakness and profuse vomiting present for the preceding week. At this time there was a definite lemon-yellow

* From the Binghamton City Hospital, Binghamton, N. Y.

tint to the skin and the breath continued to have a uremic odor. The blood pressure was 170/90 and it was advised that the patient be re-hospitalized immediately but the patient refused this until one week later. Because of the severe azotemia which was now present it was decided to try gastric intubation and lavage using tap water for lavage purposes at a rate of 100 drops per minute. She was given 1,500 cc. of 15 per cent glucose in distilled water with added vitamins intravenously and penicillin and ACTH were started. Three days following the institution of the gastric lavage the patient complained of severe weakness and she started to convulse. At that time a serum potassium level was reported as 12.9 mg. per cent and an electrocardiogram showed low and flat T-waves with a Q-T interval of 0.52 seconds. It was believed that she had both hypopotassemia and hypochloremia, the former probably being low originally as a result of her renal disease and the profuse vomiting and diarrhea, further accentuated by gastric lavage. A sodium level was then done and reported as 290 mg. per cent. At this time her urinary output was 1,300 cc. daily. Measures were immediately taken to correct the electrolyte imbalance. A polyethylene feeding tube was inserted into the stomach and she was given ammonium, potassium, calcium and sodium chloride by this route. ACTH was stopped and dilantin® was used to control the convulsions.

On September 27, 1951, the patient's condition had definitely improved and her electrocardiogram now showed a normal Q-T interval with upright T-waves of good amplitude. Two days later the therapy was again too impetuous and her face had become slightly edematous but this was alleviated soon after the sodium intake was decreased. There was continued improvement and, despite an elevated non-protein nitrogen, she was discharged from the hospital on October 9, 1951, to be followed in the attending physician's office.

The patient felt well despite an elevated non-protein nitrogen (up to 123 mg. per cent) while the blood pressure continued to be elevated to approximately 160/100. She was re-admitted to the hospital on December 12, 1951, for twenty-four hours' observation following a convulsion while receiving a blood transfusion given very slowly in order to avoid such an event. At this time the blood calcium was reported as 7.0 mg. per cent and the blood phosphorus as 5.9 mg. per cent. She was given a mild sedative but despite continued small blood transfusions, which were given slowly to avoid any untoward effects, the blood count remained low. On February 15, 1952, the patient complained of a severe vaginal discharge and it was at this time that she first noted some erosion of the skin in the interlabial folds and on the anterior aspects of both thighs. Vaginal douches and antiseptic ointment locally were advised for these conditions.

She was re-admitted to the Binghamton City Hospital on February 28, 1952, because of persistent vaginal bleeding which had been present since the onset of her menstrual period two weeks previously. On admission she complained of severe weakness, fatigue, exertional dyspnea, muscular irritability and twitchings. The excoriations about the inguinal area had become worse and they were now ulcerated and hemorrhagic. She had increased vaginal bleeding not responsive to testosterone and there was now some bleeding from the umbilicus. A biopsy of the granulomatous area revealed a non-specific necrotizing ulcer with perivascular round cell reaction of the vessels in the deeper parts of the tissue.

Four days after admission the creatinine level was reported as 14 mg. per cent and the non-protein nitrogen level as 198 mg. per cent. On March 6, 1952, the patient became short of breath and developed slight hemoptysis. The blood pressure at this time was 130/100. She had no facial edema but there were fine rales at both lung bases. Bleeding continued from the umbilicus and from the biopsied skin lesion despite the use of oxycel and pressure bandages. A chest x-ray showed cardiac enlargement both to the right and to the left and the pulmonary artery and the bronchovascular pattern was markedly accentuated. Pulmonary edema was noted as was a moderate amount of fluid at the right base. The superior vena cava and the azygos vein were prominent but no consolidation was seen and the aorta was considered normal. The patient was digitalized but she now complained of severe precordial pain and on March 10, 1952, it was believed that a precordial friction rub was present. Two days later an electrocardiogram showed a normal Q wave, a bowed-up S-T segment in leads I, II, AVL and V_4 to V_6 and a Q-T interval of 0.40 seconds. This was believed to be due to a pericarditis and the prolonged Q-T interval was probably hypokalemic in

origin. The patient was sedated and placed in an oxygen tent but on the morning of March 13, 1952, she was found dead in her bed.

At postmortem examination* the unexpected pathologic finding was located in the anterior mediastinum. From the level of the opening of the superior vena cava into the right auricle down to the diaphragm and between the parietal pericardium and the right parietal pleural fold, there was a large hematoma not involving the superior vena cava or the azygos veins. Microscopic examination of the veins running along the right wall of the parietal pericardium showed them to be thrombosed. The hemorrhage into the anterior mediastinum was secondary to thrombosis of these veins.

The remaining essential pathologic findings were those expected with chronic glomerulonephritis with uremia. The kidneys were contracted and scarred and microscopically they showed the changes typical of chronic glomerulonephritis. Bilateral lobar pneumonia involving the lower lobes was found in the lungs and the heart was diffusely enlarged. Petechial hemorrhages were present in the brain, heart, pericardium, adrenals and in the gastrointestinal tract.

COMMENT

In the case presented in this communication there were diffuse petechial hemorrhages in most of the organs but the most striking feature was the large hematoma in the anterior mediastinum. This hemorrhagic manifestation has not been described previously in the literature. In this case the hematoma was likewise a part of the hemorrhagic diathesis which caused hemorrhages in most of the organs including the skin. It is believed that the thrombosis was secondary to endothelial damage of the veins.

In Mason's series[1] of 265 cases of uremia, 20 per cent of the patients developed pericarditis. In our case the patient developed severe precordial pain with electrocardiographic changes suggestive of pericarditis and, because of the relative frequency of pericarditis in uremia, the etiology of the precordial pain appeared obvious. In retrospect we believe that the pain was due to the irritation and pressure exerted by the large amount of free blood in the anterior mediastinum since there was no evidence of pericarditis on postmortem examination.

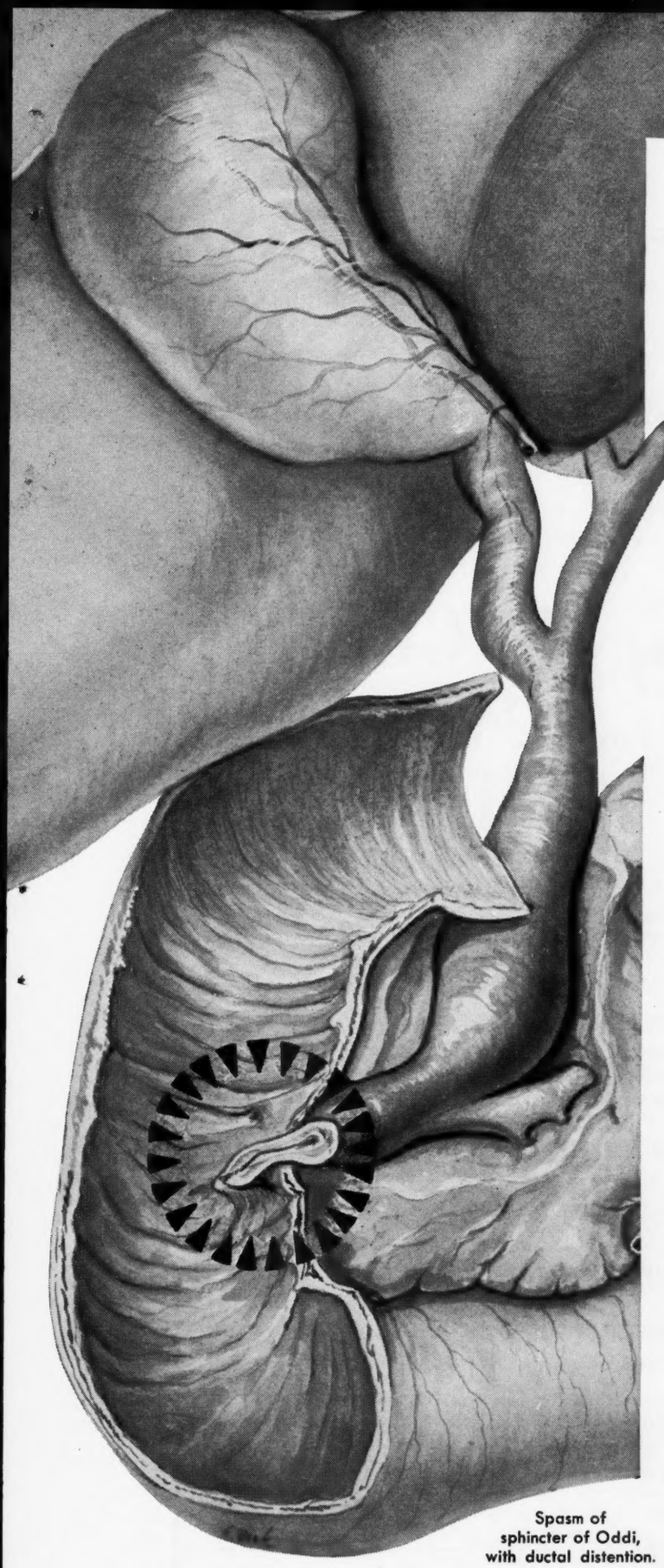
SUMMARY

A case of uremia in which the patient developed a large anterior mediastinal hematoma is presented. Hemorrhage into the anterior mediastinum can be mistaken for acute pericarditis since pericarditis is a relatively common complication of uremia.

REFERENCE

1. Mason, E. E. Gastrointestinal lesions occurring in uremia. *Ann. Int. Med.*, 37: 96, 1952.

* Done by Dr. J. S. Grewal, former pathologist, Binghamton City Hospital.



Spasm of sphincter of Oddi, with ductal distention.

Rational Therapy in Biliary Stasis and Biliary Dyskinesia with Ketochol®

Ketochol contains all four unconjugated bile acids—*not salts*

An inadequate flow of bile[1] into the intestine, caused by such conditions as severe liver disease, biliary fistulas, biliary obstruction and congenital atresia of the bile ducts, will eventually produce severe nutritional and digestive disturbances, anemia and a tendency toward abnormal bleeding.

Ketochol stimulates the flow of thin bile to "flush" the biliary passages. Ketochol relieves nausea, vomiting, pain and other symptoms of chronic inflammation of the gallbladder by its hydrocholeretic action.

Ketochol is well tolerated. The average dose is one tablet three times a day with meals, together with a suitable diet.

Ketochol is available in tablet form, 250 mg. (3¾ grains) of ketocholanic acids per tablet.

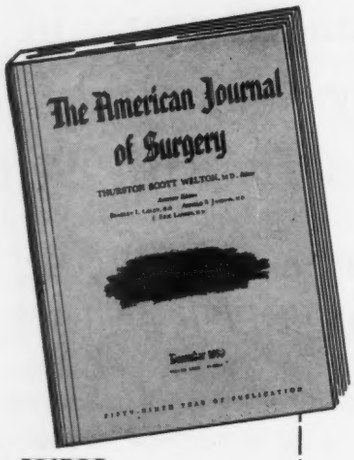
Adjunctive Antispasmodic-Sedative Therapy

Pavatrine® with Phenobarbital for selective control of smooth muscle spasm and for mild sedation of the nervous, tense patient is an excellent adjuvant in the management of biliary disorders. The average dose is one or two tablets three or four times daily, as needed.

Pavatrine with Phenobarbital contains 125 mg. (2 grains) of Pavatrine and 15 mg. (¼ grain) of phenobarbital per tablet.

1. Irvin, J. L.: The Secretion and Enterohepatic Circulation of Bile Acids: Replacement of Bile Acids in Biliary Insufficiency, North Carolina M. J. *13*:206 (April) 1952.

SEARLE *Research in the Service of Medicine*



Meat...

and the Important Role of Protein in Hemoglobin Synthesis

Although the relationship between iron and hemoglobin formation is widely appreciated, the important role played by protein in hemoglobin synthesis is relatively obscure. Nevertheless, since globin is just as much a component of the hemoglobin molecule as is iron, the continued synthesis of this protein is necessary for normal hemoglobin production.

It has recently been estimated that in the average adult 8 Gm. of globin is destroyed daily.[1] This means "that approximately 14% of the total dietary protein intake of the average adult [female] is required solely for the re-synthesis of new hemoglobin. These data reemphasize the importance of adequate protein, as well as iron, intake for the maintenance of a normal rate of hemoglobin synthesis in man."[2]

Because meat is an outstanding source of *both* iron and high quality protein, it is always recommended in generous amounts in the dietary management of hypochromic anemia. These nutritional values, as well as its significant content of B vitamins, also make meat an important component of the daily diet of normal persons.

---

1. Drabkin, D. L.: Metabolism of Hemin Chromoproteins, Physiol. Rev. *31*:345 (1951).
2. The Biosynthesis of Hemoglobin, Editorials, J.A.M.A. *150*:1223 (Nov. 22) 1952.

The Seal of Acceptance denotes that the nutritional statements regarding meat made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

WYETH PRODUCTS IN CLINICAL APPLICATION

WYCHOL® in the correction of abnormal patterns of fat metabolism.

Clinicians frequently observe noteworthy subjective improvement in patients receiving lipotropic medication for various conditions.[1,2] Empiric findings of this nature are abundantly supplemented by clinical and experimental observations indicating that: *Lipotropic substances can and do influence favorably certain abnormal patterns of lipid turnover.*

Confirmation of the value of lipotropic therapy in fatty infiltration of the liver is afforded by numerous published reports. These are perhaps best summarized by Pollak's observation that

> "The reversal of hepatic steatosis and the improvement of the patients' well-being justify fully the usage of lipotropics . . ."[5]

Effect In Atherosclerosis

A number of clinicians have reported that lipotropic factors aid in the reduction of hypercholesteremia,[6] and that their daily use favorably influences the mortality rate in coronary atherosclerosis.[7]

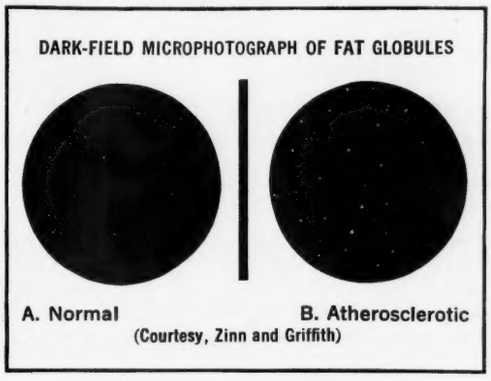
During the past few years, a great deal of experimental and clinical investigation has been directed to studies on etiologic factors in atherosclerosis. An important contributory factor is a high relative concentration of chylomicrons—fat particles 0.3 micron in diameter or larger—in the circulating blood of the fasting patient.[8,9] Recently, Labecki[10] has shown that a nutritional lipotropic regimen continued over a period of several months influenced the ratio of these lipids profoundly "in the direction of apparent normality."

Lipotropic therapy lowers the chylomicron level.[10]

A potent lipotropic combination—Syrup WYCHOL, choline and inositol, Wyeth—provides in each tablespoonful (15 cc.), 3 Gm. *choline base* (equivalent to 7.5 Gm. choline dihydrogen citrate) *plus* 0.45 Gm. inositol. WYCHOL is pleasantly flavored to encourage patient acceptance. Dosage with WYCHOL may be conveniently adjusted to suit the individual case.

WYCHOL is supplied in bottles of 1 pint and is also available as Capsules WYCHOL in bottles of 100 and 1000.

A new Syrup WYCHOL B is now available for your use. It contains WYCHOL to which has been added vitamin B_1, 2.5 mg.; vitamin B_2, 0.5 mg.; vitamin B_6, 2.5 mg., and niacinamide, 10 mg., in each 3 teaspoonfuls (15 cc.).



References

1. Eggers, H.: New York State J. Med. **51**:2255 (Oct. 1) 1951
2. Nelson, A.M.: Northwest Med. **51**:860 (Oct.) 1952
3. Pelner, L., and others: Rev. Gastroenterol. **19**:939 (Dec.) 1952
4. Cayer, D., and Cornatzer, W.E.: Gastroenterology **20**:385 (March) 1952
5. Pollak, O.J.: Delaware State M.J. **24**:157 (June) 1952
6. Herrmann, G.R.: Texas State J. Med. **42**:260 (Aug.) 1946
7. Morrison, L.M.: Am. Heart J. **42**:538 (Oct.) 1951
8. Moreton, J.R.: J. Lab. & Clin. Med. **35**:373 (Mar.) 1950
9. Zinn, W.J., and Griffith, G.C.: Am. J. M. Sc. **220**:597 (Dec.) 1950
10. Labecki, T.D.: Proc. Gerontol. Soc., Wash., D.C. (Sept. 6) 1952: Abst. J. Gerontol. **7**: No. 3 (July) 1952

Wyeth®

PHILADELPHIA 2, PA.

FOR YOUR PATIENT

with Bronchial Asthma, Hay Fever, Urticaria

LUASMIN

Brewer

CAPSULES
PLAIN
(for prompt action)

TABLETS
ENTERIC-COATED
(for delayed action)

One capsule and one tablet, taken at bedtime will provide almost all patients with eight hours relief and sleep. The relief can be sustained by using the capsules during the day at 4 hour intervals as required.

Each capsule and enteric-coated tablet contains:

Theophylline Sodium Acetate .....(3 gr.) 0.2 Gms.
Ephedrine Sulfate .....(½ gr.) 30 Mg.
Phenobarbital Sodium .....(½ gr.) 30 Mg.

Capsules and tablets in half the above potency available for children and mild cases in adults

For samples just send your Rx blank marked 13LU10

Brewer EST. 1852

BREWER & COMPANY, INC.
WORCESTER 8, MASSACHUSETTS U.S.A.

AMA is Local and National WMA is International

They speak for you

Just as the American Medical Association has fought socialized medicine on the American scene, so the World Medical Association has blocked the efforts of the International Labor Organization to introduce socialized medicine on a worldwide scale.

WMA is also actively engaged in REPRESENTING YOUR INTERESTS by conducting surveys and taking part in discussions and decisions on such vital issues as:

—standards of medical education
—the effect of social security on medical practice
—the status and distribution of hospitals
—medical manpower
—requirements for practice
—the adoption of a Universal International Code of Medical Ethics

WMA has also cooperated with the International Red Cross, the World Health Organization and similar groups in:

—giving assistance to underdeveloped countries
—the distribution of scientific, social and economic medical information
—holding forums for the discussion of international medical affairs
—calling the First World Conference on Medical Education

you can't afford to be out of touch with an organization that represents you in such varied and vital matters

JOIN NOW

what affects world medicine affects you

WMA is Approved by the American Medical Association

Dr. Louis H. Bauer, Secretary-Treasurer
U.S. Committee, Inc., World Medical Association
345 East 46th Street, New York 17, New York

I desire to become an individual member of the World Medical Association, United States Committee, Inc., and enclose a check for $_____, my subscription as a:

_____Member —$ 10.00 a year
_____Life Member —$500.00 (No further assessments)
_____Sponsoring Member—$100.00 or more per year

Signature_____

Address_____

_____

(*Contributions are deductible for income tax purposes*)

Make checks payable to the U.S. COMMITTEE, WORLD MEDICAL ASSOCIATION

this is your only voice in world medicine

6 to choose from to meet individual vitamin needs

to meet current requirements

COMBEX® KAPSEALS®

provide the additional amounts of vitamin B-complex factors needed during periods of growth, of pregnancy, of lactation, and of stress.

for combined B-complex and C deficiencies

COMBEX WITH VITAMIN C KAPSEALS

combat frequently coexisting deficiencies of factors of the vitamin B-complex and of vitamin C.

high potency B-complex and C

THERA-COMBEX* KAPSEALS

provide factors of the vitamin B-complex and of vitamin C in high potencies needed for intensive vitamin therapy.

*Trade Mark

for rapid increase in B-complex reserves

COMBEX PARENTERAL

particularly suitable when oral administration is impracticable or unreliable. Also useful for certain types of anemia.

when faulty digestion is an added liability

TAKA-COMBEX® KAPSEALS

provide Taka-Diastase,® potent starch digestant, plus nutritional supplementation with factors of the vitamin B-complex and with vitamin C.

to facilitate administration

TAKA-COMBEX ELIXIR

for flexibility of dosage and for convenient administration. Particularly useful in older and in younger patients.

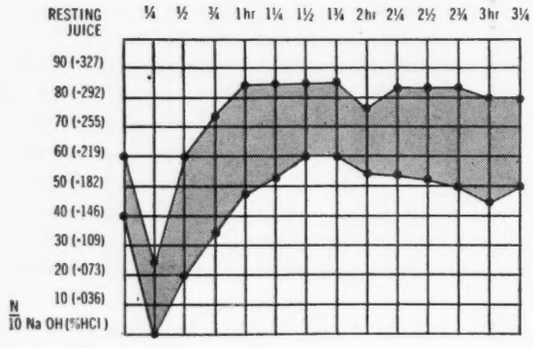
Detailed information from your pharmacist or from the Parke-Davis representative who calls on you. Literature available upon request.

MEDICAMENTA VERA

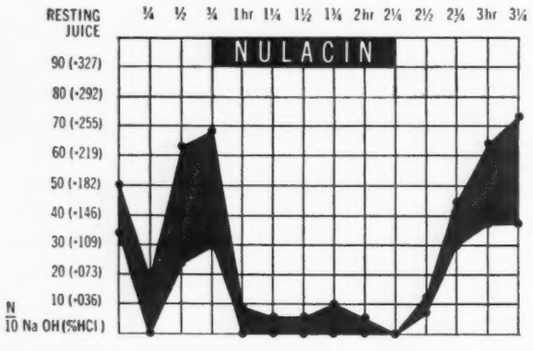
Parke, Davis & Company

DETROIT, MICHIGAN

provides continuous maintained gastric anacidity required for rapid healing



GASTRIC ANALYSIS. Superimposed gruel fractional test-meal curves of five patients with peptic ulcer.



GASTRIC ANALYSIS. Same patients, two days later, showing the neutralizing effect of sucking Nulacin tablets (three an hour).

in peptic ulcer

Nulacin

NULACIN quickly and conveniently achieves—in the ambulant patient—the intragastric state most conducive to continued freedom from pain and to rapid ulcer healing.[1, 2]

It accomplishes this desirable objective—maintained anacidity—because the tablet is not chewed but is allowed to remain in the mouth and dissolve slowly.

Its contained antacids thus are released slowly, at a rate sufficient to neutralize virtually all HCl as it is formed.

Because of this maintained anacidity patients report a sense of well-being not experienced with other antacid medications.

Each tablet, prepared from milk combined with dextrins and maltose, incorporates magnesium trisilicate, 3.5 gr., magnesium oxide, 2.0 gr., calcium carbonate, 2.0 gr., magnesium carbonate, 0.5 gr., ol. menth. pip., q.s. The palatable taste of Nulacin meets with immediate patient acceptance.

In active ulcer flare-ups, two to three tablets per hour, starting one-half to one hour after each meal, are prescribed. During quiescent periods, the suggested dosage is two tablets between meals.

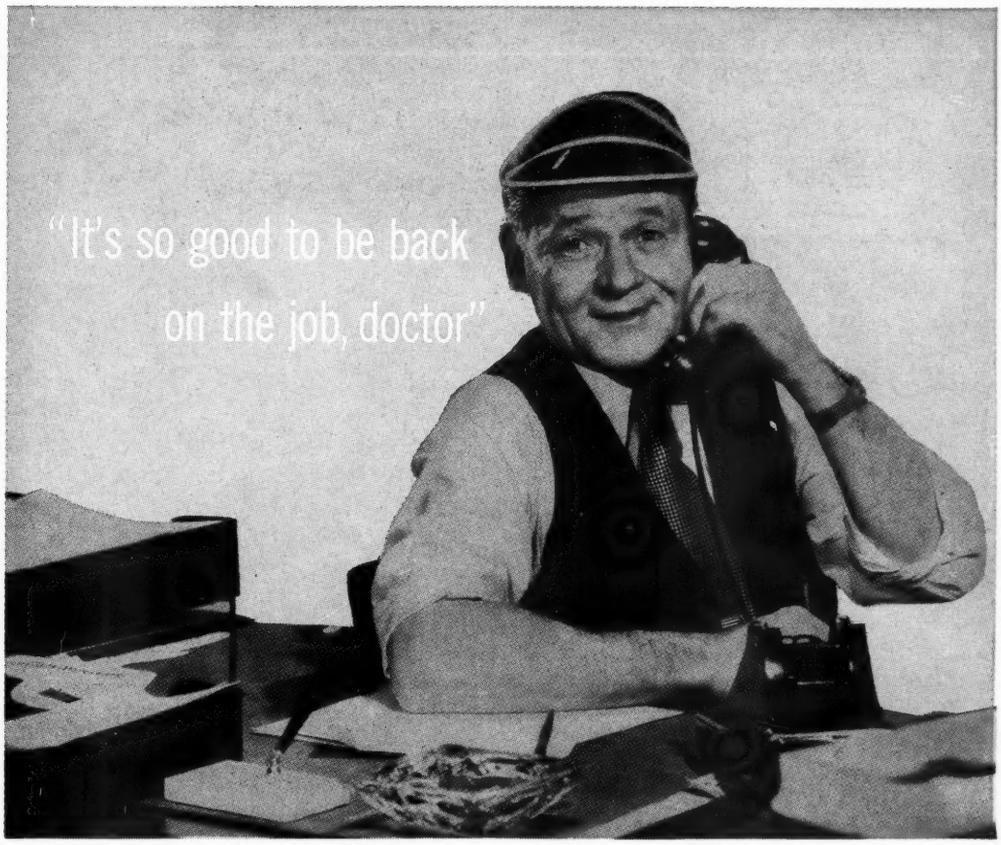
Indicated in active and quiescent peptic ulcer, gastritis, gastric hyperacidity. Available through all pharmacies in tubes of 25 tablets.

1. Douthwaite, A. H., and Shaw, A. B.: The Control of Gastric Acidity, Brit. M. J. 2:180 (July 26) 1952.

2. Douthwaite, A. H.: Medical Treatment of Peptic Ulcer, M. Press 227:195 (Feb. 27) 1952.

HORLICKS CORPORATION
RACINE, WISCONSIN

Pharmaceutical Division

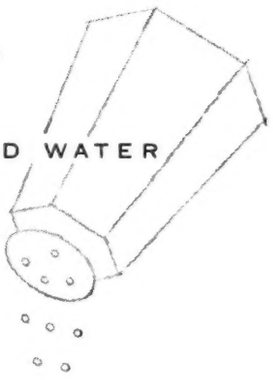


TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN

NORMAL OUTPUT OF SODIUM AND WATER



PRESCRIBE NEOHYDRIN whenever there is retention of sodium and water except in acute nephritis and intractable oliguric states. You can balance the output of salt and water against a more physiologic intake by individualizing dosage. From one to six tablets a day, as needed.

PRESCRIBE NEOHYDRIN in bottles of 50 tablets. There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research

Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

PHOTOGRAPH BY RUZZI GREEN

"My throat sure feels better"

TRACINETS®

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

ACTIONS AND USES: With TRACINETS you can readily relieve afebrile mouth and minor throat irritations in young patients—and in older ones, too. Acting together, bacitracin and tyrothricin are truly synergistic. Soothing local relief is afforded by benzocaine. In severe throat infections TRACINETS Troches, by their local action, supplement antibiotic injections.

QUICK INFORMATION: Each TRACINETS Troche contains 50 units of bacitracin, 1 mg. of tyrothricin and 5 mg. of benzocaine. Available in vials of 12.

Upjohn

mixed surface infections . . .

Each gram contains 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base).

Available: Ointment in ½ oz. and 1 oz. tubes, and 4 oz. jars. Cream in ½ oz. tubes.

The Upjohn Company, Kalamazoo, Michigan

Myciguent

Trademark Reg. U. S. Pat. Off.

CREAM OR OINTMENT

physiologic relief of "morning sickness"

EMETROL®

[PHOSPHORATED CARBOHYDRATE SOLUTION]

Kinney®

In a well-controlled study, Crunden and Davis[1] recently found that EMETROL abolished or reduced the severity of pregnancy nausea in 78.8 percent of 123 patients . . . *usually within 24 hours.* In contrast, a placebo of similar taste and appearance proved moderately beneficial in only 15.6 percent of 122 controls.

EMETROL contains balanced amounts of levulose and dextrose in coacting association with orthophosphoric acid, stabilized at an optimally adjusted pH. Containing no antihistaminics, barbiturates, or narcotics, it is a safe, inexpensive, *physiologic agent* which may be given freely without stimulating or depressing the patient. Its value for a given patient can be readily appraised by the physician in a minimum of time.[1] Dosage for nausea of pregnancy — 2 tablespoonfuls taken *undiluted* immediately on arising, repeated as required if nausea recurs.

IMPORTANT: EMETROL must *not* be diluted or followed by any liquids for at least 15 minutes.

Also beneficial in vomiting associated with intestinal "flu," motion sickness, and nausea due to drug therapy or anesthesia.

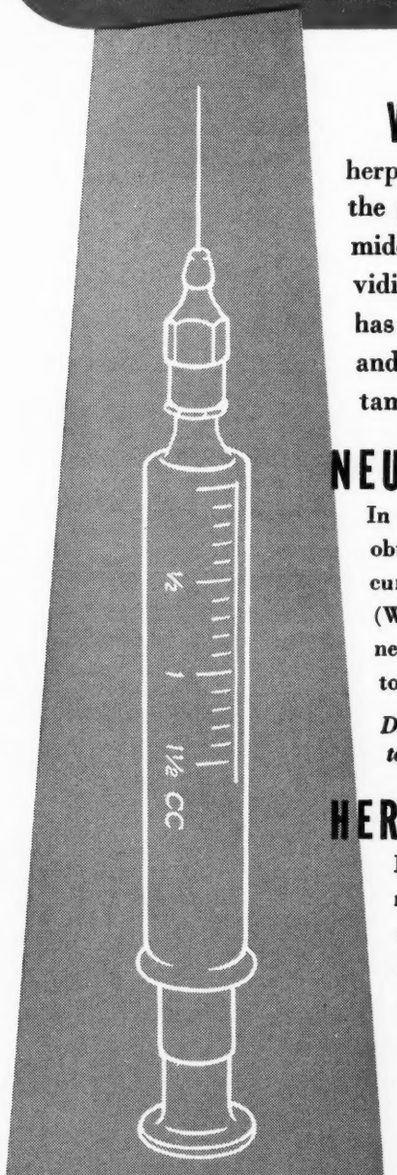
SUPPLIED: Bottles of 3 fl. oz. and 16 fl. oz. through all pharmacies. *Literature and Samples on Request.*

1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.

KINNEY & COMPANY • COLUMBUS, INDIANA

PROTAMIDE

FOR THE PATIENT SEEKING RELIEF FROM NERVE ROOT PAIN



WHEN the disturbing and painful symptoms of herpes zoster, or the stinging distress of neuritis brings the patient to you, quick relief is expected. Protamide helps solve this therapeutic problem by providing prompt and lasting relief in most cases. This has been established by published clinical studies, and on the valid test of patient-response to Protamide therapy in daily practice.

NEURITIS (Sciatic—Intercostal—Facial)

In a recent study* of 104 patients, complete relief was obtained in 80.7% with Protamide. 49 were discharged as cured after 5 days of therapy with no subsequent relapse. (Without Protamide, the usual course of the type of neuritis in this series has been found to be three weeks to over two months.)

Dosage: one 1.3 cc. ampul intramuscularly, daily for five to ten days.

HERPES ZOSTER

A study* of fifty patients with Protamide therapy resulted in excellent or satisfactory response in 78%. (No patient who made a satisfactory recovery suffered from postherpetic neuralgia.) Thirty-one cases of herpes zoster were treated with Protamide in another study.* Good to excellent results were obtained in 28.

Dosage: one 1.3 cc. ampul intramuscularly, daily for one to four or more days.

* *A folio of reprints of these studies will be sent on request.*

SHERMAN LABORATORIES
BIOLOGICALS • PHARMACEUTICALS
WINDSOR DETROIT 15, MICH. LOS ANGELES

A Striking Example of Drug Complementation...

This combination of Hypotensive Agents *Leads to*

- Dramatic Symptomatic Improvement
- Better Hypotensive Response
- Reduced Dosage Requirements
- Fewer Side Effects

AN ORIGINAL RIKER RESEARCH PRODUCT containing alkaloids from *Rauwolfia serpentina* and *Veratrum viride*

Rauwiloid + Veriloid®

The calming, relaxing, and moderate hypotensive effect of Rauwiloid (a standardized alkaloidal extract from Rauwolfia serpentina), when combined with the more powerful hypotensive influence of Veriloid (a standardized alkaloidal extract from Veratrum viride), leads to a unique type of drug complementation. The patient's Veriloid requirement is decreased, side effects, if present, disappear, and a striking hypotensive response is produced. Not only are the diastolic and systolic pressures lowered significantly, but at the same time, the patient feels better, headache and dizziness disappear, and tachycardia, when present, is replaced by mild bradycardia.

On the basis of this apparent synergism, Rauwiloid+Veriloid leads to excellent results in moderate, severe, and resistant hypertension. Each tablet contains 1 mg. of Rauwiloid and 3 mg. of Veriloid. Average dose, one tablet three or four times daily, ideally after meals, at intervals of not less than four hours. Available in bottles of 100, an average month's supply.

In Mild and Moderate Hypertension

Rauwiloid alone

As shown in a recent study,* Rauwiloid administered alone produces excellent results in early, mild, or labile hypertension. In this condition, the blood pressure is significantly reduced, a sense of well-being is quickly engendered, and mild bradycardia soon replaces tachycardia. Toxic reactions do not occur, even when the amount of drug administered is three or four times the usual dose. Side actions are surprisingly rare. Thus Rauwiloid becomes the medication of choice in uncomplicated mild and moderate hypertension. Initial dose, 4 mg. (2 tablets) once daily; maintenance dose, 2 mg. daily. Supplied in bottles of 60 tablets, an average month's supply.

*Ford, R. V.; Livesay, W. R.; Miller, S. I., and Moyer, J. H.: Preliminary Observation of Rauwolfia Therapy of Hypertension, M. Rec. & Ann., in press.

Rauwiloid, an original Riker development, represents the alseroxylon alkaloidal fraction of *Rauwolfia serpentina*. Each batch is tested in dogs for its ability to produce sedation, drop in blood pressure, and bradycardia. Hence pharmacologic uniformity is assured.

BIBLIOGRAPHY

Ford, R. V., and Moyer, J. H.: Preliminary Observations of Rauwiloid-Hexamethonium Combined Therapy of Hypertension, Am. Heart J., in press.

Wilkins, R. W., and Judson, W. E.: The Use of Rauwolfia Serpentina in Hypertensive Patients, New England J. Med. *248*:48 (Jan. 8) 1953.

Wilkins, R. W.; Judson, W. E., and Stanton, J. R.: Preliminary Observations on Rauwolfia Serpentina in Hypertensive Patients, Proc. New England Cardiovas. Soc., 1951-1952, p. 34.

Vakil, R. J.: A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension, Brit. Heart J. *11*:350 (Oct.) 1949.

RIKER LABORATORIES, INC. 4500 BEVERLY BLVD. • LOS ANGELES 49, CALIF.

11 reasons to consider MANDELAMINE in urinary infections

1 Controls most common urinary infections in 3 to 14 days.[1,2,3]

2 Bacteriostatic and bactericidal action is of approximately the same order as sulfonamides or streptomycin.[4,5,6,7] Effective against gram-positive and gram-negative organisms.

3 Bacteria do not develop resistance.[5,8,9] For this reason, Mandelamine is particularly suitable for chronic conditions in which permanent sterilization cannot usually be expected because of an obstruction, stone, or indwelling catheter. In such cases, Mandelamine usually renders the patient asymptomatic.

4 Although Mandelamine has been widely prescribed for more than ten years, no serious toxic effects, such as blood dyscrasias or crystalluria, have been reported. This lack of toxicity in therapeutic dosage makes Mandelamine especially useful in patients who are not under close supervision. The only contraindication is renal insufficiency.

5 Side effects, such as nausea and vomiting, are rare. Mandelamine does not cause monilial infections responsible for diarrhea, proctitis, vaginitis, and stomatitis.

6 No risk of sensitizing the patient to drugs which may be life-saving in overwhelming infections.

7 Organisms resistant to antibiotics retain their normal susceptibility to Mandelamine.[4,9]

8 Can be given concurrently with antibiotics or sulfonamides. In virulent infections accompanied by high fever, antibiotics or sulfonamides may exert a rapid antibacterial effect and reduce the fever. Continued therapy with Mandelamine usually brings the infection under control, while avoiding the expense and possible untoward effects of prolonged use of antibiotics or sulfonamides.

9 No supplementary acidification required (except in presence of urea-splitting organisms which are responsible for only a small percentage of urinary infections).

10 Regulation of diet or fluid intake is unnecessary.

11 Inexpensive.

ADULT DOSAGE: 3 to 4 tablets t.i.d.
CHILDREN: in proportion.
0.25 gram enteric coated tablets, bottles of 120.

1. Beckman, H., and Tatum, A. L.: Wisconsin M. J. 51:185, 1952. 2. Carroll, G., and Allen, H. N.: J. Urology 55:674, 1946. 3. Kirwin, T. J., and Bridges, J. P.: Am. J. Surgery 52:477, 1941. 4. New and Nonofficial Remedies, A.M.A., 1952. 5. Scudi, J. V., and Duca, C. J.: J. Urology 61:459, 1949. 6. Scudi, J. V., and Reinhard, J. F.: J. Lab. & Clin. Med. 33:1304, 1948. 7. Duca, C. J., and Scudi, J. V.: Proc. Soc. Exper. Biol. & Med. 66:123, 1947. 8. Schloss, W. A.: Connecticut M. J. 14:994, 1950. 9. Knight, V., and others: Antibiotics & Chemotherapy 2:615, 1952.

NEPERA CHEMICAL CO., INC.
Pharmaceutical Manufacturers
Nepera Park, Yonkers 2, N. Y.

in the treatment of Hypertension

Prolonged effect of mannitol hexanitrate

lowers pressure for 4 to 6 hours

New and Nonofficial Remedies: A.M.A. Council on Pharmacy and Chemistry, J. B. Lippincott, p. 243, 1953.

Marked diuretic action of theophylline

facilitates sodium excretion

Med. Times *81*:266 (Apr.) 1953.

Phenobarbital for relaxation without hypnosis

most useful for promoting daytime relaxation

J.A.M.A. *147*:1311 (Dec.) 1951.

Ascorbic acid + rutin for capillary protection

help to maintain capillary integrity

Delaware State M. J. *22*:283 (Oct.) 1950.

Semhyten®

BRINGS THE PRESSURE DOWN SLOWLY  **SAFELY**

Complete Medication for the Hypertensive

Each Semhyten Capsule contains:	Phenobarbital..¼ gr. (15 mg.)
Mannitol Hexanitrate....½ gr. (30 mg.)	Rutin .....10 mg.
Theophylline .....1½ gr. (0.1 Gm.)	Ascorbic Acid .....15 mg.

Supplied: In bottles of 100, 500 and 1000 pink-top capsules.

The S. E. MASSENGILL Company • Bristol, Tennessee

SYNANDROTABS*	Methyl Testosterone, U.S.P., Tablets 10 mg. and 25 mg.
SYNANDRETS*	Testosterone, U.S.P., Transmucosal Tablets 10 mg. and 25 mg.
SYNANDROL*	Testosterone Propionate, U.S.P., in Sesame Oil 25 mg., 50 mg. and 100 mg. per cc.; in single-dose disposable STERAJECT® cartridges and in 10 cc. multiple-dose vials
SYNANDROL*-F	Testosterone, U.S.P., in Aqueous Suspension 25 mg., 50 mg. and 100 mg. per cc.; in 10 cc. multiple-dose vials
DIOGYNETS*	Estradiol, U.S.P., Transmucosal Tablets 0.125 mg., 0.25 mg. and 1.0 mg.
DIOGYN*-E	Ethinyl Estradiol Tablets 0.02 mg., 0.05 mg. and 0.5 mg.
DIOGYN*	Estradiol, U.S.P., in Aqueous Suspension 0.25 mg. and 1.0 mg. per cc.; in single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
DIOGYN*-B	Estradiol Benzoate, U.S.P., in Sesame Oil 0.33 mg. and 1.0 mg. per cc.; in 10 cc. multiple-dose vials
ESTRONE	Estrone, U.S.P., in Aqueous Suspension 2 mg. and 5 mg. per cc.; in 10 cc. multiple-dose vials
SYNGESTROTABS*	Ethisterone, U.S.P., Tablets 10 mg., 25 mg. and 50 mg.
SYNGESTRETS*	Progesterone, U.S.P., Transmucosal Tablets 10 mg., 20 mg. and 50 mg.
SYNGESTERONE* IN SESAME OIL	Progesterone, U.S.P., in Sesame Oil 10 mg., 25 mg., 50 mg. and 100 mg. per cc.; in single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
SYNGESTERONE* IN AQUEOUS SUSPENSION	Progesterone, U.S.P., in Aqueous Suspension 25 mg. and 50 mg. per cc.; in 10 cc. multiple-dose vials
COMBANDRIN*	Estradiol Benzoate, U.S.P., 1 mg. per cc. and Testosterone Propionate, U.S.P., 20 mg. per cc. in Sesame Oil. In single-dose disposable STERAJECT cartridges and in 10 cc. multiple-dose vials
COMBANDRETS*	Estradiol, U.S.P., 1 mg. and Testosterone, U.S.P., 10 mg. per Transmucosal Tablet
NEODROL*	Stanolone in Aqueous Suspension 50 mg. per cc.; in 10 cc. multiple-dose vials

*TRADEMARK

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

Greaseless, long-lasting SKIN PROTECTION

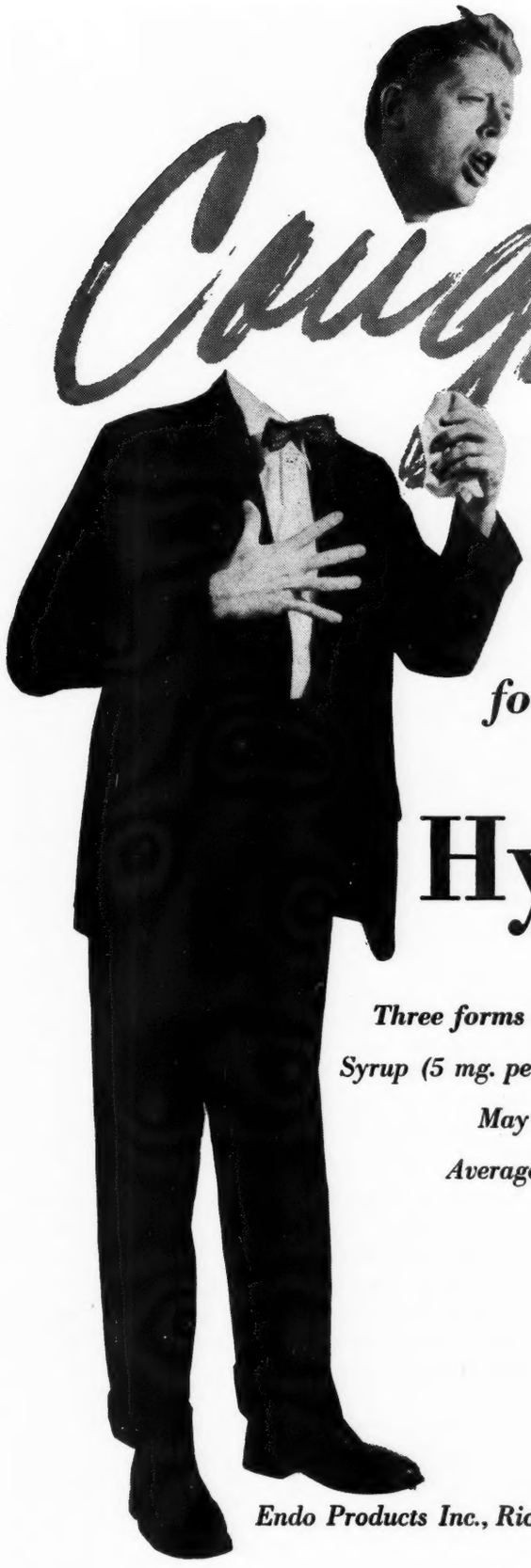
for industrial dermatoses and contact allergies

NOT removed by ordinary washing, COVICONE Cream offers the long-lasting qualities often desired in the management of industrial and allergic dermatoses. An entirely new formula, COVICONE is a special *plasticized* combination of silicone, nitrocellulose and castor oil. Applied to the skin, it forms an effective but invisible physical barrier against sensitizing and irritating agents.

Suspended in a vanishing cream base, COVICONE is easy to apply, is not sticky or greasy. To build up the protective layer, the cream is applied twice daily for 10 days to two weeks. Effective protection can then be maintained indefinitely with a single application every one or two days. COVICONE is indicated wherever skin protection is desired from environmental substances; there are no contraindications except premature application on wet, exudative lesions. At pharmacies in one-ounce tubes and one-pound jars. Abbott

new plasticized cream withstands washing

COVICONE CREAM
TRADE MARK
(Abbott's Protective Skin Cream)



Coughing

your head off!

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

for effective cough therapy

Hycodan® BITARTRATE

(Dihydrocodeinone Bitartrate)

Three forms available: Oral Tablets (5 mg. per tablet), Syrup (5 mg. per teaspoonful), Powder (for compounding). May be habit forming; narcotic blank required. Average adult dose 5 mg. Literature on request.

Endo®

Endo Products Inc., Richmond Hill 18, N.Y.

an improved approach to ideal hypotensive therapy

Low toxicity. The only hypotensive drug that causes no dangerous reactions, and almost no unpleasant ones.

Slow, smooth action. The hypotensive effect is more stable than with other agents. Critical adjustment of dosage is unnecessary. Tolerance to the hypotensive effect has not been reported.

Well suited to patients with relatively mild, labile hypertension. A valuable adjunct to other agents in advanced hypertension.

Bradycardia and mild sedation increase its value in most cases. Symptomatic improvement is usually marked.

Convenient, safe to prescribe

The usual starting dose is 2 tablets twice daily. If blood pressure does not begin to fall in 7 to 14 days, and the medication is well tolerated, the dose may be safely increased. Should there be a complaint of excessive sleepiness, the dose should be reduced. Some patients are adequately maintained on as little as one tablet per day.

Dosage of other agents (veratrum or hydralazine) used in conjunction with Raudixin must be carefully adjusted to the response of the patient. If Raudixin is added to another maintenance regimen, the usual dose is applicable, and it is often possible to reduce the dose of the other agent or agents.

Supplied **in tablets of 50 mg., bottles of 100 and 1000.**

SQUIBB

RAUDIXIN
SQUIBB RAUWOLFIA SERPENTINA
Tablets

'RAUDIXIN' IS A TRADEMARK

NEW...council-accepted oral anticoagulant *(not a coumarin derivative)* with a wide range of safety

HEDULIN®

(Brand of Phenindione, 2-phenyl-1,3-indandione)

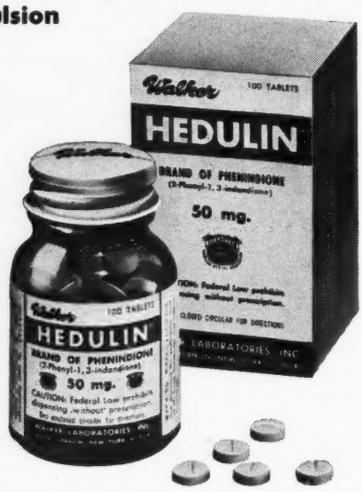
ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
- **HEDULIN is rapidly excreted—therapeutic effect dissipated within 24-48 hours if withdrawal becomes necessary**
- **HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours**
- **HEDULIN requires fewer prothrombin determinations—only one in 7 to 14 days, after maintenance dose is established**
- **HEDULIN's anticoagulant action is rapidly reversed by vitamin K_1 emulsion**

DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

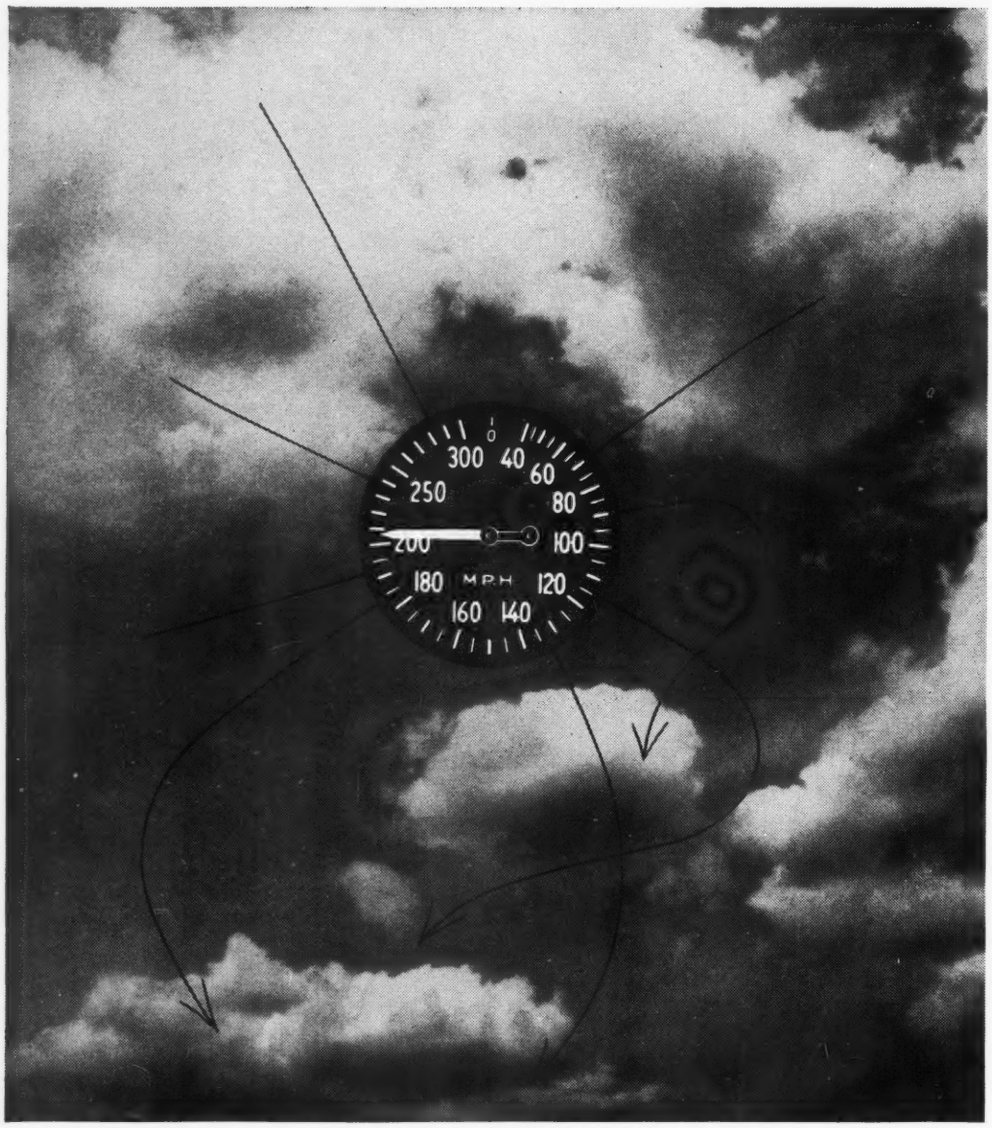
Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.



Complete literature to physicians on request

Walker **LABORATORIES, INC., MOUNT VERNON, N. Y.**

*Registered trademark of Walker Laboratories, Inc.



Air velocity—200 miles per hour

In coughing, the expulsive air speed often irritates mucosal tissue and induces more coughing. Phenergan Expectorant is valuable in arresting this vicious cycle. It relieves local irritation on contact . . . combats any existing allergic component of cough . . . when prescribed for night cough, promotes uninterrupted, restful sleep.

At your option: with or without codeine

PHENERGAN® EXPECTORANT

PROMETHAZINE EXPECTORANT

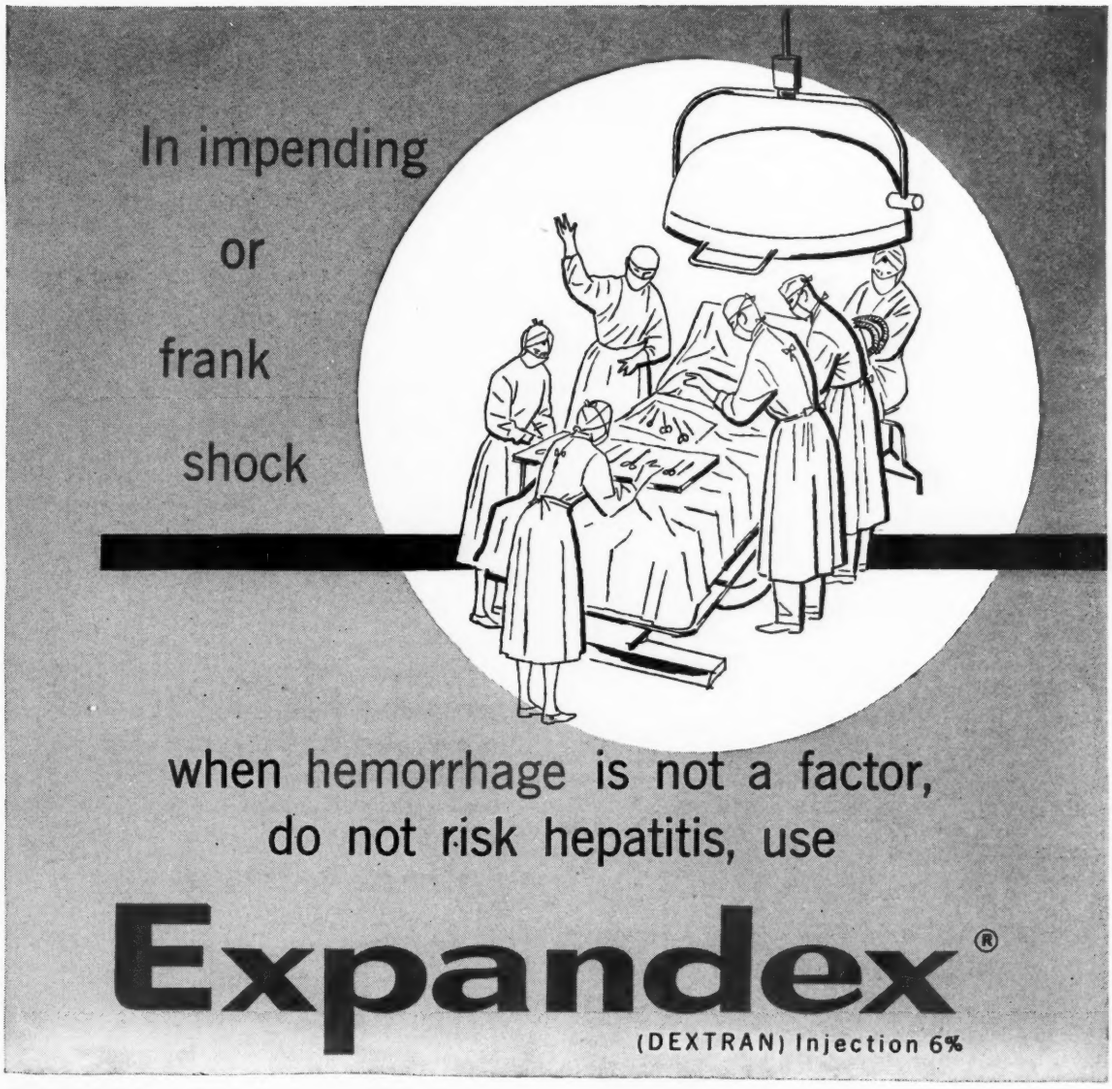
WITH CODEINE* **PLAIN (without codeine)**

SUPPLIED: Bottles of 1 pint

*Exempt Narcotic

Wyeth®

Philadelphia 2, Pa.



When hemorrhage is not a factor in producing shock, or when the blood loss does not exceed 30%, all danger of hepatitis can be avoided when Expandex is used as an emergency measure to restore effective plasma volume. Containing 6% dextran in isotonic sodium chloride solution, Expandex is sterile, therefore cannot transmit the virus of hepatitis. Expandex can also serve as the sole means of overcoming circulatory failure in shock due to surgery, trauma and burns. It offers the added advantages of instant availability because it is in solution, non-interference with blood typing and cross-matching, and virtually complete elimination from the organism through excretion or metabolism. Expandex, the first clinically acceptable dextran solution produced in the United States, is supplied in 250 cc. and 500 cc. flasks; the latter is also supplied with a sterile administration set complete with needle and airway cannula.

CSC Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION • 260 MADISON AVE., NEW YORK 16, N. Y.

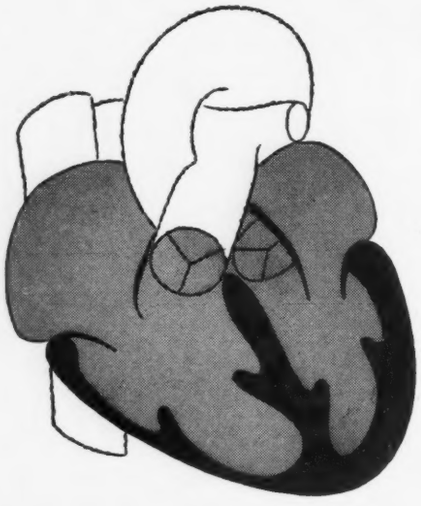
NOW

the first intramuscular digitoxin

DIGITALINE NATIVELLE®

INTRAMUSCULAR

for dependable digitalization and maintenance when the oral route is unavailable



DIGITALINE NATIVELLE INTRAMUSCULAR
is indicated for patients who are comatose, nauseated or uncooperative, or whose condition precludes the use of the oral route.

DIGITALINE NATIVELLE INTRAMUSCULAR
provides all the unexcelled virtues of its parent oral preparation.

Steady, predictable absorption.

Equal effectiveness, dose-for-dose with oral DIGITALINE NATIVELLE.

Easy switch-over to oral medication.

Clinical investigation has shown that DIGITALINE NATIVELLE INTRAMUSCULAR is "effective in initiation and maintenance of digitalization. A satisfactory therapeutic effect was obtained with minimal local and no undesirable systemic effects."*

DIGITALINE NATIVELLE INTRAMUSCULAR – 1-cc. and 2-cc. ampules, boxes of 6 and 50. Each cc. provides 0.2 mg. of the original digitoxin – DIGITALINE NATIVELLE.

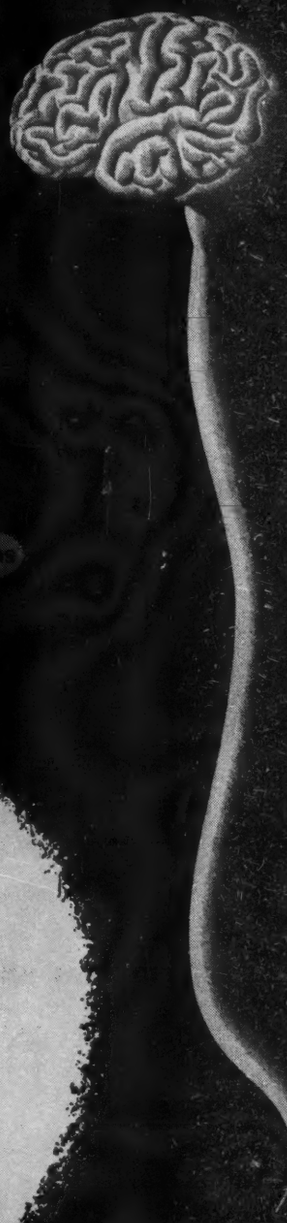
*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent, Am. Heart J. 44:787, 1952.

Literature and samples available on request.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

central nervous "pacifier"...

Mephate®



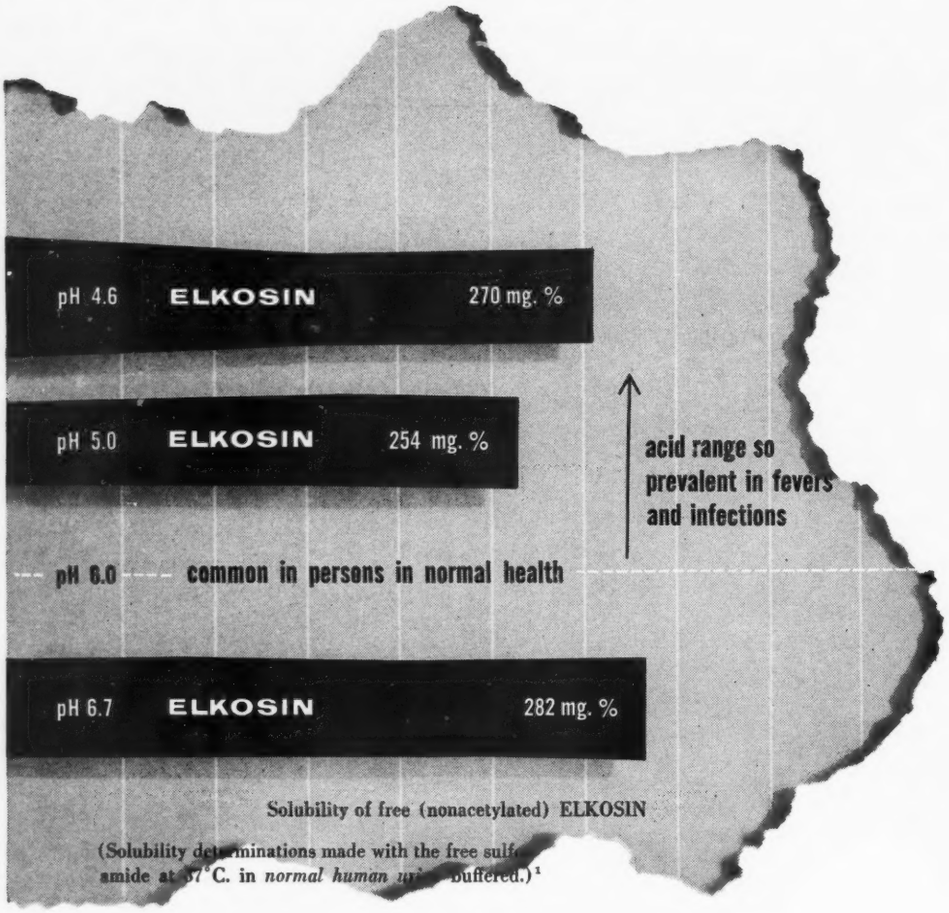
In Mephate 'Robins', the clinical usefulness of mephenesin per os has been significantly heightened by the inclusion of glutamic acid hydrochloride, which improves absorption and enhances effectiveness for many patients otherwise unresponsive.* Provides a relaxant effect on skeletal muscle spasm; an ameliorating effect on tremor; and a relief of anxiety without dimming consciousness. Particularly helpful in abnormal neuro-muscular conditions such as rheumatic disorders, disc syndromes and cerebral palsy; alcoholism, anxiety tension states and psychiatric states.

In each Mephate Capsule, 0.25 Gm. mephenesin — with 0.30 Gm. glutamic acid hydrochloride.
Adult dosage starts at 2 capsules 3 or 4 times a day, preferably with food or liquids.

*Hermann, I. F., and Smith, R. T.: Jl.-Lancet 71:271 (July), 1951.

A. H. ROBINS CO., INC. · RICHMOND 20, VA.

Ethical Pharmaceuticals of Merit since 1878



high solubility where it counts

in the acid pH range
so prevalent in fevers
and infections

alkalis not needed

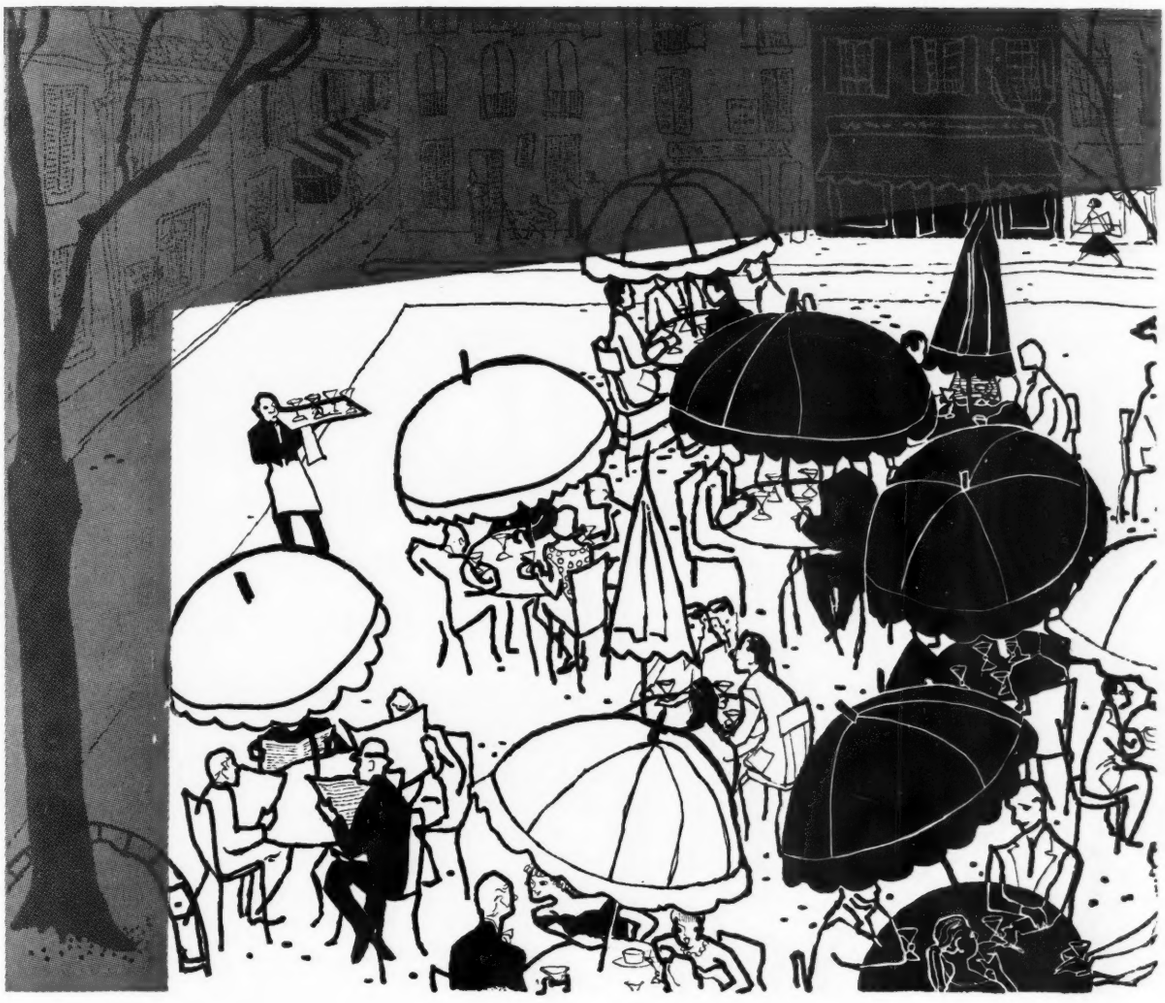
ELKOSIN®

SULFISOMIDINE CIBA

a new advance in sulfonamide safety

tablets 0.5 Gm., double-scored. Bottles of 100 and 1000
suspension in syrup 0.25 Gm. per teaspoonful (4 cc.). Pints.

1. Ziegler, J. B.; Bagdon, R. E., and Shabica, A. C.: To be published.



They'd crowd an outdoor cafe...

all the patients who represent the 44 uses

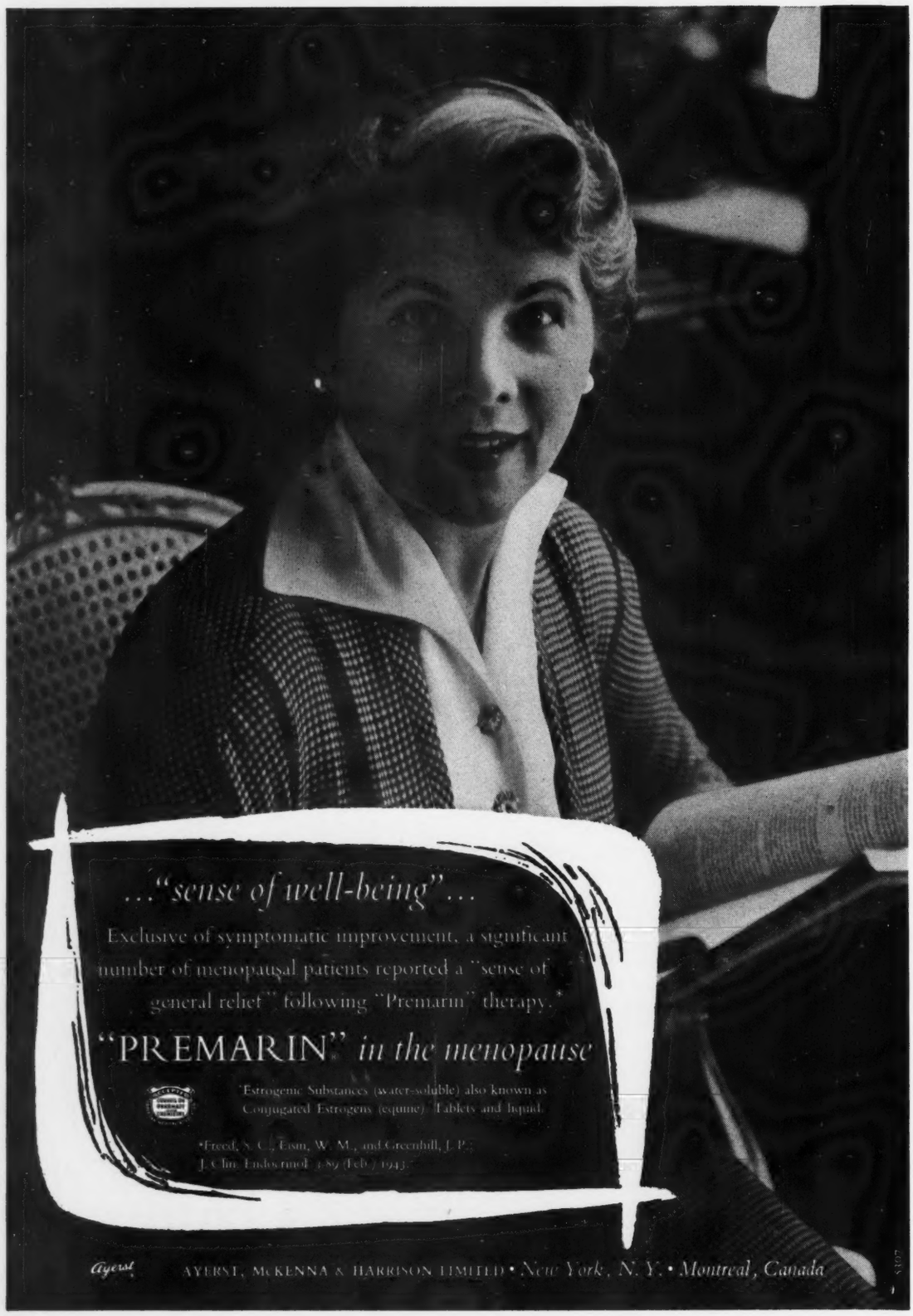
for short-acting NEMBUTAL®

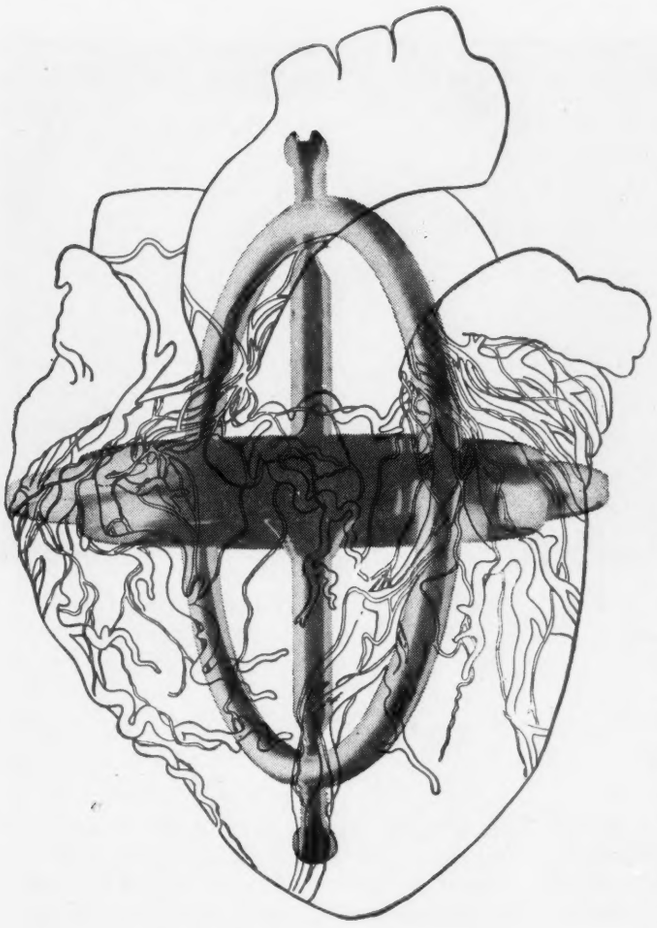
44 PATIENTS? Just look in the picture above. You'll find them all. And with every NEMBUTAL patient, with every NEMBUTAL use, these are the facts that you'll find the same:

1. *Short-acting* NEMBUTAL (*Pentobarbital, Abbott*) *can produce any desired degree of cerebral depression—from mild sedation to deep hypnosis.*
2. *The dosage required is small—only about one-half that of many other barbiturates.*
3. *There's less drug to be inactivated, shorter duration of effect, wide margin of safety and little tendency toward morning-after hangover.*
4. *In equal oral doses, no other barbiturate combines quicker, briefer, more profound effect.*

All are sound enough reasons for your prescription to call for short-acting NEMBUTAL. How many uses have *you* tried? Abbott

1-212


...“sense of well-being”...
Exclusive of symptomatic improvement, a significant number of menopausal patients reported a “sense of general relief” following “Premarin” therapy.*
“PREMARIN” in the menopause
Estrogenic Substances (water-soluble) also known as Conjugated Estrogens (equine). Tablets and liquid.
*Freed, S. C., Eisin, W. M., and Greenhill, J. P.: J. Clin. Endocrinol. 3:89 (Feb.) 1943.
Ayerst
AYERST, McKENNA & HARRISON LIMITED • New York, N.Y. • Montreal, Canada



CARDIAC GYROSCOPE

Balance—true balance—
in controlling both frequency
and force of the cardiac impulse
and in uniformity of therapeutic
effect is achieved with—

Digoxin 'B.W. & CO.'®

a pure, stable, crystalline glycoside isolated from Digitalis lanata

- first signs of action apparent within an hour after initial oral dose
- relief of symptoms in about six hours
- full digitalization within first 24 hours
- eliminated fast enough to permit rapid control of toxicity in cases of overdosage
- no fleeting peaks of action
- a single daily dose maintains most patients

For routine digitalization and maintenance

'Tabloid'® brand Digoxin 0.25 mg., bottles of 100, 500 and 1000

For rapid digitalization

'Wellcome'® brand Digoxin Injection 0.5 mg. in 1 cc., boxes of 12 and 100

Burroughs Wellcome & Co. (U. S. A.) Inc., *Tuckahoe 7, N. Y.*

What enriched bread is doing for America today.

Enriched bread, representing the bulk of bread consumed today, makes significant nutrient contributions to the dietary and to the nutritional health of the American people.[1] Bread cannot be regarded merely as an energy food. Instead, it is an important purveyor of many nutrients which a large proportion of our population would never receive in adequate amounts if enriched bread were not available on so large and wide a scale.[2] Here is what modern day enriched bread provides:

VITAMINS: Containing specified amounts of thiamine, riboflavin, and niacin, enriched bread makes a significant contribution to the satisfaction of these vitamin requirements. Enriched bread has played an important role in virtually eliminating frank deficiency diseases and materially reducing subclinical deficiency states resulting from dietary inadequacies in these essentials.[2]

MINERALS: By providing substantial amounts of calcium[3] and of added iron, modern enriched bread goes far in satisfying the needs for these substances. For example, six ounces of bread on the average provides approximately 15 per cent of the day's recommended calcium allowance for adults and 38 per cent of the iron allowance.

PROTEIN: The protein of commercial bread is of high biologic value because it is a mixture of wheat flour protein and milk protein, the latter derived from added nonfat milk solids.[4] One pound of enriched bread furnishes about 39 Gm. of protein.

ECONOMY: At its present day low price, bread represents an outstanding nutritional "buy." It provides not only generous amounts of essential nutrients, but also readily available food energy. These features truly make enriched bread one of America's *basic foods.*

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

REFERENCES

1. Sebrell, W. H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
2. Flour and Bread Enrichment, 1949-50: Prepared by The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.
3. Data furnished by the Laboratories of the American Institute of Baking, Chicago, Illinois.
4. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 8. New York, The Macmillan Company, 1952, pp. 212; 597-600; 646.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

Advertisers Index

October, 1953


PRICE REDUCTION
20% PRICE REDUCTION* ON
50-MG. TABLET
20% ADDITIONAL SAVING* WITH
NEW 100-MG. TABLET
Now supplied as tablets
in 4 different potencies
Gilbert